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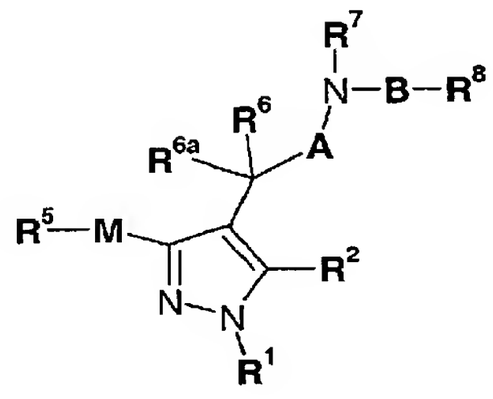
(54) Title: PYRAZOLE DERIVATIVES AS GNRH INHIBITORS



(I)

(57) Abstract: The invention relates to a group of novel thieno-pyrrole compounds of Formula (I); wherein: R^1, R^2, R^5, R^6, R^{6a}, R^7, R^8, A, B and M are as defined in the specification, which are useful as gonadotrophin releasing hormone antagonists. The invention also relates to pharmaceutical formulations of said compounds, methods of treatment using said compounds and to processes for the preparation of said compounds.

PYRAZOLE DERIVATIVES AS GNRH INHIBITORS

The present invention relates to compounds which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

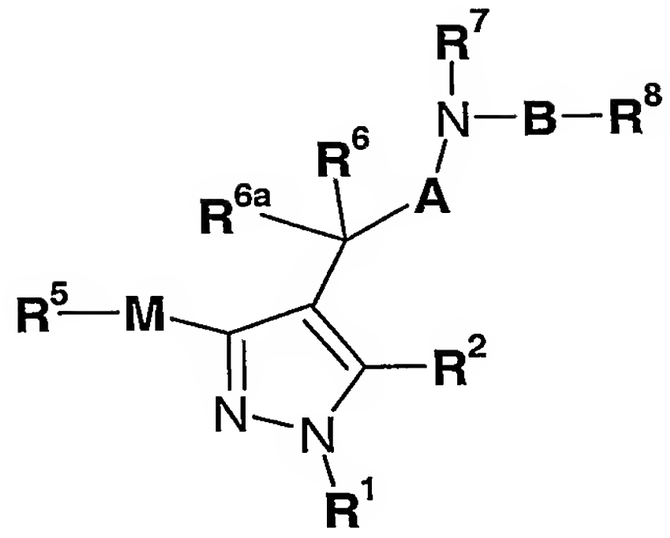
Gonadotropin releasing hormone (GnRH) is a decapeptide that is secreted by the hypothalamus into the hypophyseal portal circulation in response to neural and/or chemical stimuli, causing the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary. GnRH is also known by other names, including gonadoliberin, LH releasing hormone (LHRH), FSH releasing hormone (FSH RH) and LH/FSH releasing factor (LH/FSH RF).

GnRH plays an important role in regulating the action of LH and FSH (by regulation of their levels), and thus has a role in regulating the levels of gonadal steroids in both sexes, including the sex hormones progesterone, oestrogens and androgens. More discussion of GnRH can be found in WO 98/5519 and WO 97/14697, the disclosures of which are incorporated herein by reference.

It is believed that several diseases would benefit from the regulation of GnRH activity, in particular by antagonising such activity. These include sex hormone related conditions such as sex hormone dependent cancer, benign prostatic hypertrophy and myoma of the uterus. Examples of sex hormone dependent cancers are prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The following disclose compounds purported to act as GnRH antagonists: WO 97/21435, WO 97/21703, WO 97/21704, WO 97/21707, WO 55116, WO 98/55119, WO 98/55123, WO 98/55470, WO 98/55479, WO 99/21553, WO 99/21557, WO 99/41251, WO 99/41252, WO 00/04013, WO 00/69433, WO 99/51231, WO 99/51232, WO 99/51233, WO 99/51234, WO 99/51595, WO 99/51596, WO 00/53178, WO 00/53180, WO 00/53179, WO 00/53181, WO 00/53185, WO 00/53602, WO 02/066477, WO 02/066478, WO 02/06645 and WO 02/092565.

It would be desirable to provide further compounds, such compounds being GnRH antagonists. Thus, according to the first aspect of the invention there is provided a compound of Formula (I),

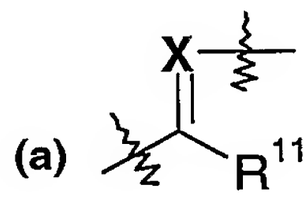


Formula (I)

wherein

A represents a direct bond or optionally substituted C_{1-5}alkylene;

B is a group of Formula (II):



Formula (II);

wherein at position (a) Formula (II) is attached to the nitrogen atom and the group **X** is attached to $\mathbf{R^8}$;

M is $-(CH_2)_{0-2}$-O-;

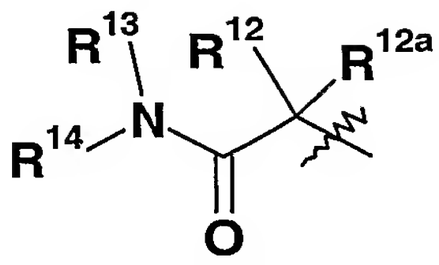
$\mathbf{R^1}$ represents hydrogen; optionally substituted C_{1-8}alkyl; or $(CH_2)_{\mathbf{b}}$-$\mathbf{R^a}$, wherein

$\mathbf{R^a}$ represents C_{3-8}cycloalkyl and **b** is zero or an integer from 1 to 6;

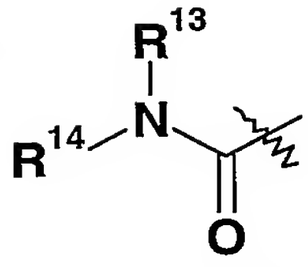
$\mathbf{R^2}$ represents an optionally substituted mono- or bi-cyclic aromatic ring structure wherein the optional substituents are selected from cyano, $N\mathbf{R^3R^{3a}}$, optionally substituted C_{1-8}alkyl, optionally substituted C_{1-8}alkoxy or halo;

$\mathbf{R^3}$ and $\mathbf{R^{3a}}$ are independently selected from hydrogen; optionally substituted C_{1-8}alkyl and optionally substituted aryl;

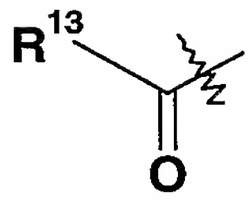
$\mathbf{R^5}$ is selected from an optionally substituted 3 to 8 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S; or a group of formula **III-a**; **III-b**; **III-c**; **III-d**; **III-e; III-f**, **III-g** , **III-h**, **III-i** or: **III-j**;



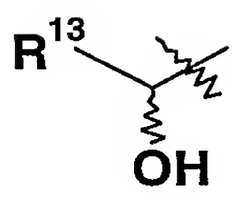
III-a



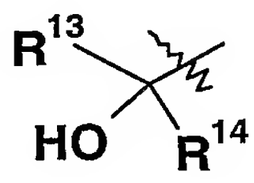
III-b



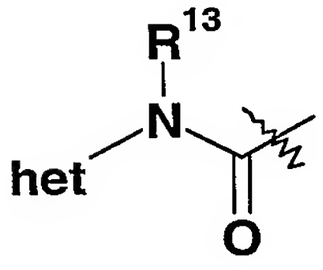
III-c



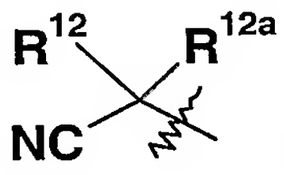
III-d



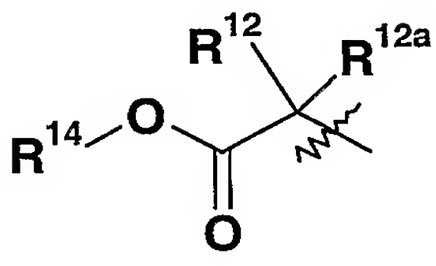
III-e



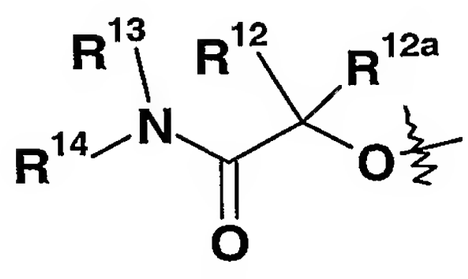
III-f



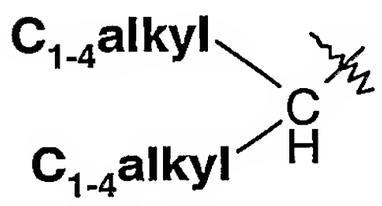
III-g



III-h



III-i



III-j

wherein **het** represents an optionally substituted 3 to 8 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

$\mathbf{R^6}$ and $\mathbf{R^{6a}}$, are independently selected from hydrogen and optionally substituted $C_{1\text{-}8}$alkyl;

or $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ together represent carbonyl;

$\mathbf{R^7}$ represents hydrogen or optionally substituted $C_{1\text{-}8}$alkyl;

or $\mathbf{R^6}$–A–N–$\mathbf{R^7}$ together from an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 3 further heteroatoms independently selected from O, N and S, and $\mathbf{R^{6a}}$ represents hydrogen and optionally substituted $C_{1\text{-}8}$alkyl;

X and $\mathbf{R^8}$ are selected from:

(i) **X** represents N and $\mathbf{R^8}$ is selected from:

cyano, hydrogen, hydroxy, -O-$\mathbf{R^b}$, –N$\mathbf{R^b}\mathbf{R^c}$ –C(O)O-$\mathbf{R^b}$, –CON$\mathbf{R^b}\mathbf{R^c}$ or NH-C(O)-$\mathbf{R^b}$, where $\mathbf{R^b}$ and $\mathbf{R^c}$ are independently selected from hydrogen and $C_{1\text{-}4}$alkyl optionally substituted with hydroxy, amino, N-$C_{1\text{-}4}$alkylamino, N,N-di-$C_{1\text{-}4}$alkylamino, HO-$C_{2\text{-}4}$alkyl-NH- or HO-$C_{2\text{-}4}$alkyl-N($C_{1\text{-}4}$alkyl)-;

(ii) **X** represents CH and $\mathbf{R^8}$ represents NO_2; and

(iii) **X**-$\mathbf{R^8}$ represents O;

$\mathbf{R^{11}}$ is a group of the formula: N($\mathbf{R^9}\mathbf{R^{10}}$) wherein $\mathbf{R^9}$ represents hydrogen, aryl, an optionally substituted 3- to 10 membered heterocyclic ring or optionally-substituted

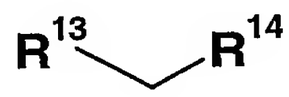
C_{1-8}alkyl and $\mathbf{R^{10}}$ represents hydrogen or optionally substituted C_{1-8}alkyl; or the structure N($\mathbf{R^9R^{10}}$) represents an optionally-substituted 3- to 10 membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;

$\mathbf{R^{12}}$ and $\mathbf{R^{12a}}$ are independently selected from hydrogen or optionally substituted C_{1-8}alkyl; or $\mathbf{R^{12}}$ and $\mathbf{R^{12a}}$ together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring;

$\mathbf{R^{13}}$ and $\mathbf{R^{14}}$ are selected from:

(i) $\mathbf{R^{13}}$ is selected from hydrogen; optionally substituted C_{1-8}alkyl; optionally substituted aryl; -$\mathbf{R^d}$-Ar, where $\mathbf{R^d}$ represents C_{1-8}alkylene and Ar represents optionally substituted aryl; and optionally substituted 3 to 8 membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and $\mathbf{R^{14}}$ is selected from hydrogen; optionally substituted C_{1-8}alkyl and optionally substituted aryl;

(ii) where $\mathbf{R^5}$ represents a group of formula **III-a , III-b** or **III-i**, then the group N$\mathbf{R^{13}}$(-$\mathbf{R^{14}}$) represents an optionally substituted 3 to 8 membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

(iii) where $\mathbf{R^5}$ represents structure **III-e**, then the group  represents an optionally substituted 3 to 8 membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

or a salt, pro-drug or solvate thereof.

According to a further feature of the first aspect of the invention there is provided a pharmaceutical formulation comprising a compound of Formula (I), or salt, pro-drug or solvate thereof, and a pharmaceutically acceptable diluent or carrier.

According to a further feature of the first aspect of the invention there is provided the following uses of a compound of Formula (I), or salt, pro-drug or solvate thereof:

(a) the use in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity;

(b) the use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinizing hormone by the pituitary gland of the patient; and

(c) the use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient,

preferably a sex hormone related condition selected from prostate cancer and pre-menopausal breast cancer.

According to a further aspect of the invention there is provided a method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering a compound of Formula (I), or salt, pro-drug or solvate thereof, to a patient.

Whilst pharmaceutically-acceptable salts of compounds of the invention are preferred, other non-pharmaceutically-acceptable salts of compounds of the invention may also be useful, for example in the preparation of pharmaceutically-acceptable salts of compounds of the invention.

Whilst the invention comprises compounds of the invention, and salts, pro-drugs or solvates thereof, in a further embodiment of the invention, the invention comprises compounds of the invention and salts thereof.

In the present specification, unless otherwise indicated, an **alkyl**, **alkylene** or **alkenyl** moiety may be linear or branched.

The term "**alkylene**" refers to the group $-CH_2-$. Thus, C_8 alkylene for example is $-(CH_2)_8-$.

The term **"aryl"** refers to phenyl or naphthyl.

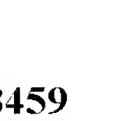
The term **"carbamoyl"** refers to the group $-CONH_2$.

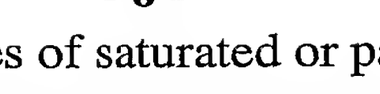
The term "**halo**" refers to fluoro, chloro, bromo or iodo.

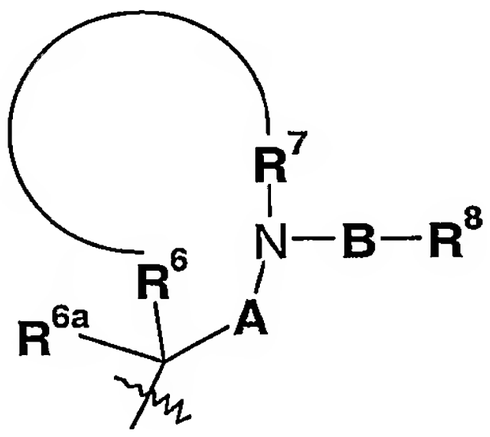
The term "**heterocyclyl**" or "**heterocyclic ring**" refers to a 5-10 membered aromatic mono or bicyclic ring or a 5-10 membered saturated or partially saturated mono or bicyclic ring, said aromatic, saturated or partially unsaturated rings containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. Examples of 5- or 6-membered aromatic heterocyclic rings include pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. A 9 or 10 membered bicyclic aromatic heterocyclic ring is an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuranyl, benzimidazolyl, benzthiophenyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, indolyl, pyridoimidazolyl, pyrimidoimidazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, phthalazinyl,

cinnolinyl and naphthyridinyl. Examples of saturated or partially saturated heterocyclic rings include pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, dihydropyridinyl and dihydropyrimidinyl. This definition further comprises sulphur-containing rings wherein the sulphur atom has been oxidised to an S(O) or S(O2) group.

The term "**aromatic ring**" refers to a 5-10 membered aromatic mono or bicyclic ring optionally containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur. Examples of such "aromatic rings" include: phenyl, pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. Preferred aromatic rings include 'phenyl, thienyl and pyridyl.

The symbol  denotes where the respective group is linked to the remainder of the molecule.

For the avoidance of doubt, when  together form an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 3 further heteroatoms independently selected from O, N and S, then the groups shown cyclise to form a nitrogen-containing heterocyclic ring, i.e



, optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S.

Examples of **C_{1-8}alkyl** include: methyl, ethyl, propyl, isopropyl, butyl, *iso*-butyl, *tert*-butyl and 2-methyl-pentyl; example of **C_{1-8}alkylene** include: methylene, ethylene and 2-methyl-propylene; examples of **C_{1-8}alkoxy** include methoxy, ethoxy and butyloxy; examples of **N-C_{1-4}alkylamino** include N-methylamino and N-ethylamino; examples of **N,N-di-C_{1-4}alkylamino**, examples of **HO-C_{2-4}alkyl-NH** include hydroxymethylamino hydroxyethylamino and hydroxypropyamino, examples of **HO-C_{2-4}alkyl-N(C_{1-4}alkyl)** include N-methyl-hydroxymethylamino, N-ethyl-hydroxyethylamino, and N-propyl-hydroxypropyamino.

It is to be understood that, insofar as certain of the compounds of the invention may

exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of antagonizing gonadotropin releasing hormone (GnRH) activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, activity of these compounds may be evaluated using the standard laboratory techniques referred to hereinafter.

The invention also relates to any and all tautomeric forms of the compounds of the different features of the invention that possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

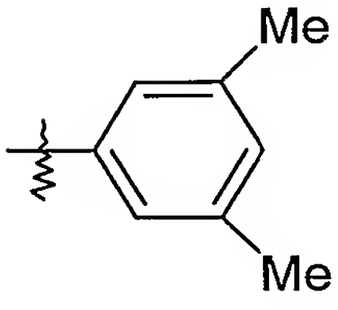
Preferred compounds of Formula (I) are those wherein any one of the following or a combination of the following apply.

Preferably **A** represents optionally substituted C_{1-5}alkylene. Further preferably C_{1-4}alkylene. Most preferably methylene or ethylene.

Preferably **M** is $-CH_2-O-$.

Preferably $\mathbf{R^1}$ represents hydrogen or optionally substituted C_{1-6}alkyl. More preferably $\mathbf{R^1}$ represents hydrogen, methyl, ethyl or *tert*-butyl. Most preferably $\mathbf{R^1}$ represents hydrogen.

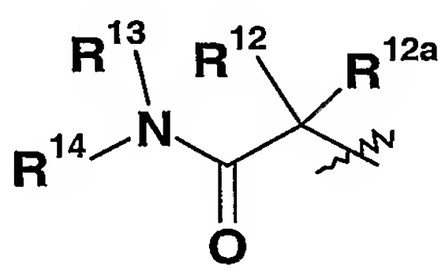
Preferably $\mathbf{R^2}$ represents an optionally substituted monocyclic aromatic ring structure wherein the optional substituents are selected from cyano, $N\mathbf{R^eR^f}$, optionally substituted C_{1-8}alkyl (preferably, C_{1-4}alkyl, eg, methyl or ethyl), optionally substituted C_{1-8}alkoxy (preferably, C_{1-6}alkoxy, eg, methoxy, ethoxy or *tert*-butoxy) or halo (eg, F, Br or Cl) wherein $\mathbf{R^e}$ and $\mathbf{R^f}$ are independently selected from hydrogen, C_{1-6}alkyl or aryl. Further preferably $\mathbf{R^2}$ is optionally substituted phenyl wherein the optional substituents are selected from cyano, $N\mathbf{R^eR^f}$, optionally substituted C_{1-4}alkyl, optionally substituted C_{1-6}alkoxy, F, Br or Cl wherein $\mathbf{R^e}$ and $\mathbf{R^f}$ are as defined above. Yet further preferably $\mathbf{R^2}$ is optionally substituted phenyl wherein the optional substituents are selected from methyl, ethyl, methoxy, ethoxy, *tert*-butoxy, F or Cl. Most preferably $\mathbf{R^2}$ represents



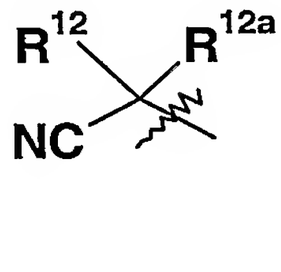
wherein Me represents methyl. Preferably $\mathbf{R^2}$ bears 1, 2 or 3 substituents.

Preferably $\mathbf{R^3}$ and $\mathbf{R^{3a}}$ are independently selected from hydrogen; optionally substituted $C_{1\text{-}6}$alkyl and , optionally substituted aryl . Further preferably $\mathbf{R^3}$ and $\mathbf{R^{3a}}$ are independently selected from methyl, ethyl, *tert*-butyl and phenyl.

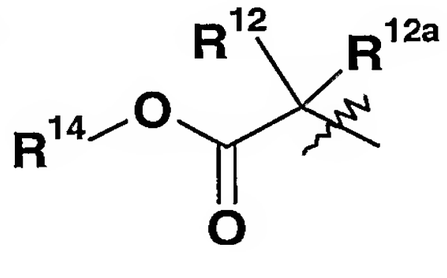
Preferably $\mathbf{R^5}$ is selected from a group of formula **III-a** , **III-g**, **III-h**, or **III-i** or: **III-j**



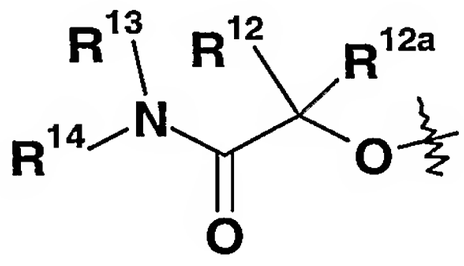
III-a



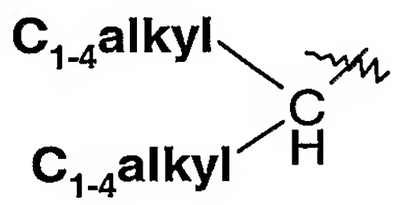
III-g



III-h

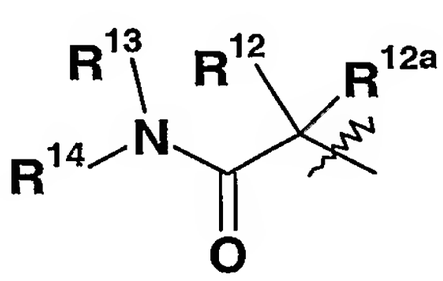


III-i

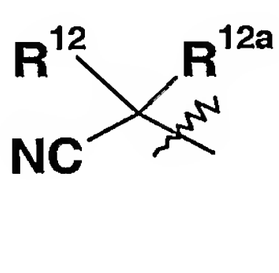


III-j

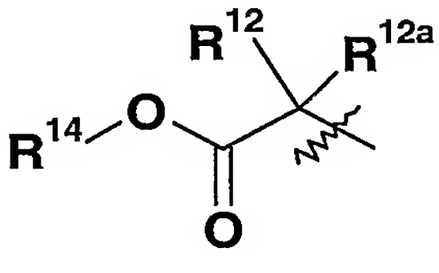
Further preferably $\mathbf{R^5}$ is selected from one of the following groups:



III-a

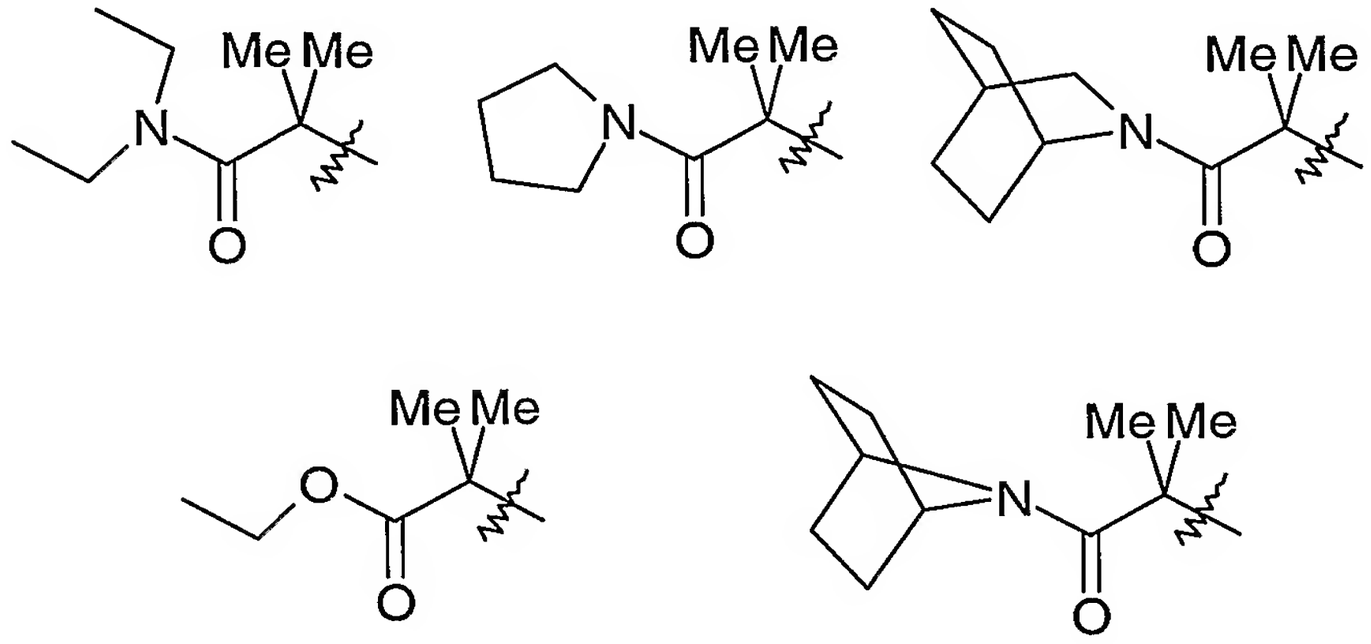


III-g



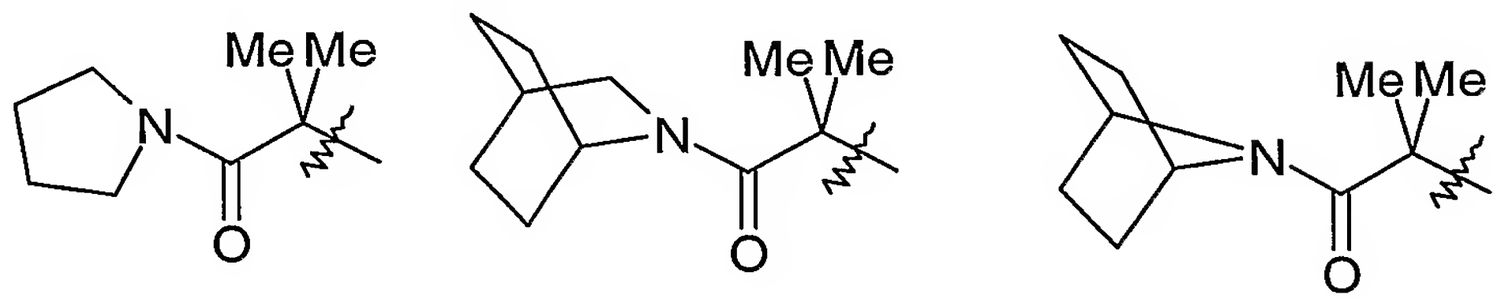
III-h

Yet further preferably $\mathbf{R^5}$ is selected from one of the following groups:



wherein Me represents methyl.

Most preferably $\mathbf{R^5}$ is selected from one of the following groups:



In one embodiment, $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ each represent hydrogen and **A** represents C_{1-4}alkylene (preferably methylene).

In a further embodiment of the invention $\mathbf{R^6}$ represents hydrogen, $\mathbf{R^{6a}}$ represents methyl, and **A** represents C_{1-4}alkylene (preferably methylene).

Preferably $\mathbf{R^7}$ is selected from hydrogen or optionally-substituted C_{1-6}alkyl. Further preferably $\mathbf{R^7}$ represents hydrogen, methyl, ethyl or *tert*-butyl.

Preferably **X** and $\mathbf{R^8}$ represent either:-

(a) **X** represents N and $\mathbf{R^8}$ represents cyano or –C(O)O-$\mathbf{R^b}$; or

(b) **X** represents N and $\mathbf{R^8}$ represents hydrogen.

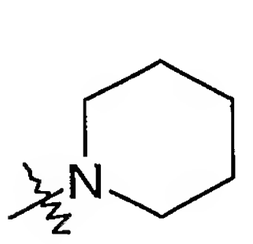
Further preferably **X** represents N and $\mathbf{R^8}$ represents cyano or –C(O)O-$\mathbf{R^b}$; wherein $\mathbf{R^b}$ represents C_{1-6}alkyl;

In a further embodiment of the invention **X** represents N and $\mathbf{R^8}$ represents -CON$\mathbf{R^b}\mathbf{R^c}$ wherein $\mathbf{R^b}$ and $\mathbf{R^c}$ are as defined above.

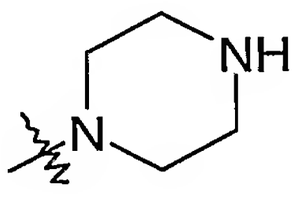
Preferably $\mathbf{R^9}$ comprise part of the group N($\mathbf{R^9}\mathbf{R^{10}}$) or is hydrogen, optionally substituted aryl, an optionally substituted 3- to 10 membered heterocyclic ring or optionally substituted C_{1-4}alkyl wherein the optional substituents are selected from: hydroxy, amino,

nitro, cyano, optionally-substituted aryl, optionally substituted 3- to 8- membered heterocyclyl containing from 1 to 4 heteroatoms independently selected from O, N and S, -O-$\mathbf{R^b}$, C(O)N$\mathbf{R^b R^c}$, -N$\mathbf{R^b R^c}$, -N$\mathbf{R^c}$C(O)-$\mathbf{R^b}$, -C(O)N$\mathbf{R^b R^c}$, -N$\mathbf{R^c}$S(O_{0-2})$\mathbf{R^b}$, -S(O_{0-2})$\mathbf{R^b}$, wherein $\mathbf{R^b}$ and $\mathbf{R^c}$ are as defined above.

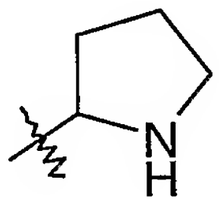
When $\mathbf{R^9}$ is a C_{1-6}alkyl group substituted by an optionally-substituted 3 to 10 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S, the heterocyclic ring is preferably selected from pyridyl, thienyl, piperidinyl, imidazolyl, triazolyl, thiazolyl, pyrrolidinyl, piperazinyl, morpholinyl, imidazolinyl, benztriazolyl, benzimidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl, furanyl, pyrrolyl, 1,3-dioxolanyl, 2-azetinyl, each of which is optionally substituted. Further preferably a group of formula **VI-a**, **VI-b**, **VI-c**, **VI-d**, **VI-e, VI-f , VI-g, VI-h, VI-i**, **VI-j** or **VI-k**:, wherein each group is optionally substituted by one or more groups selected from $\mathbf{R^{16}}$.



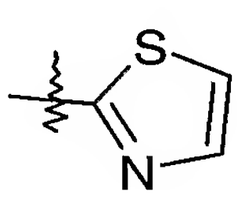
VI-a



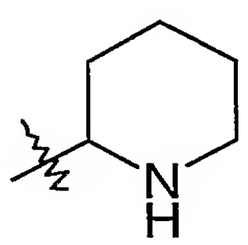
VI-b



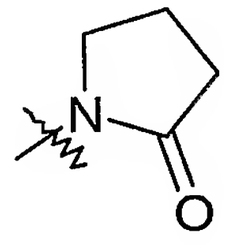
VI-c



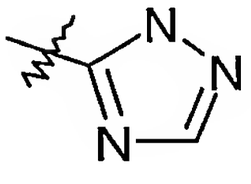
VI-d



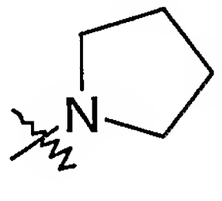
VI-e



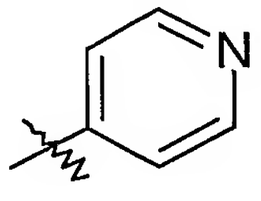
VI-f



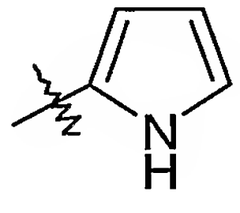
VI-g



VI-h



VI-i

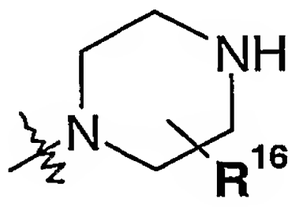


VI-j

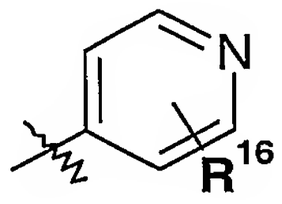
VI-k

.

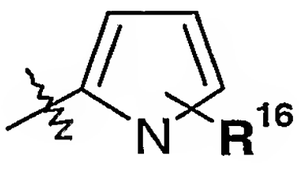
Most preferably a group of formula **VI-b**, **VI-i** or **VI-j**:



VI-b



VI-i



VI-j

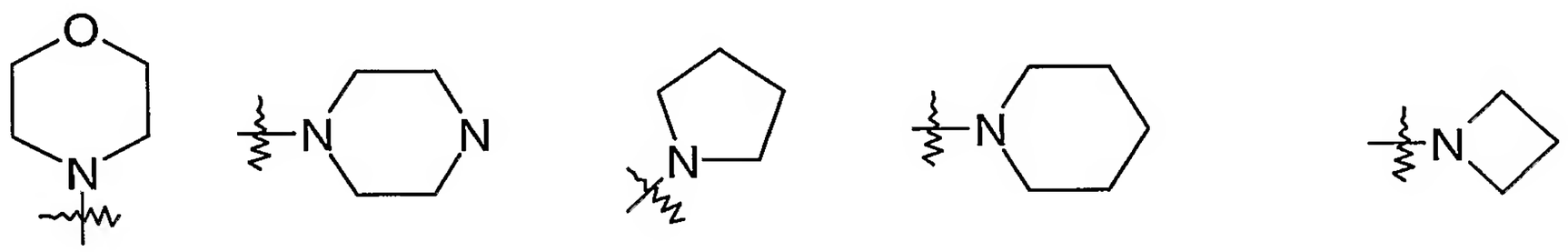
wherein

$\mathbf{R^{16}}$ represents hydrogen, aryl, a 3- to 10 membered heterocyclic ring or optionally substituted C_{1-4}alkyl wherein the optional substituents are selected from: hydroxy, amino, nitro, cyano, optionally-substituted phenyl, optionally substituted 3- to 8- membered heterocyclyl

containing from 1 to 4 heteroatoms independently selected from O, N and S, -O-$\mathbf{R^b}$, C(O)N$\mathbf{R^bR^c}$, -N$\mathbf{R^bR^c}$, -N$\mathbf{R^c}$C(O)-$\mathbf{R^b}$, -C(O)N$\mathbf{R^bR^c}$, -N$\mathbf{R^c}$S(O_{0-2})$\mathbf{R^b}$, -S(O_{0-2})$\mathbf{R^b}$, wherein $\mathbf{R^b}$ and $\mathbf{R^c}$ are as defined above;

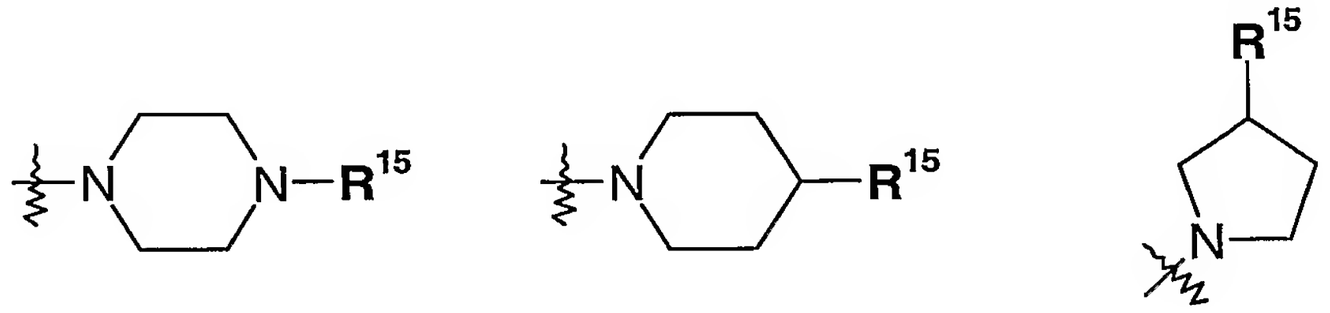
Preferably $\mathbf{R^{10}}$ comprises part of the group N($\mathbf{R^9R^{10}}$) or is optionally substituted C_{1-6}alkyl. Further preferably $\mathbf{R^{10}}$ comprises part of the group N($\mathbf{R^9R^{10}}$) or is selected from: methyl, ethyl or *tert*-butyl.

When N($\mathbf{R^9R^{10}}$) represent an optionally substituted 3- to 10- membered heterocyclic ring, N($\mathbf{R^9R^{10}}$) is preferably selected from a 5- or 6-membered monocyclic ring containing between 1 and 3 (preferably 1 or 2) heteroatoms independently selected from O, N and S. Further preferably a 5- or 6-membered monocyclic ring containing between 1 and 3 (preferably 1 or 2) heteroatoms independently selected from O, N and S, selected from pyrrolidinyl, thienyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl piperazinyl, imidazole, azetidinyl or azetinyl. Further preferably the structure N($\mathbf{R^9R^{10}}$) is a heterocyclic ring selected from an optionally-substituted group of formula, **IV-a**, **IV-b**, **IV-c**, **IV-d** and **IV-e**, wherein the optional substituents are preferably selected from the groups listed for $\mathbf{R^{15}}$ below



IV-a **IV-b** **IV-c** **IV-d** **IV-e**

Further preferably the structure N($\mathbf{R^9R^{10}}$) is selected from a group of formula **Va**, **Vb** or **Vc:**



V-a **V-b** **V-c**

Most preferably the structure N($\mathbf{R^9R^{10}}$) is a group of formula **V-c:**

$\mathbf{R^{15}}$ represents hydrogen, optionally substituted aryl, an optionally substituted 3- to 10 membered heterocyclic ring or optionally substituted C_{1-4}alkyl wherein the optional substituents on aryl, a heterocyclic ring or C_{1-4}alkyl are selected from: hydroxy, amino, nitro, cyano, halo, optionally-substituted aryl, optionally substituted 3- to 8- membered

heterocyclyl containing from 1 to 4 heteroatoms independently selected from O, N and S, -O-$\mathbf{R^b}$, C(O)N$\mathbf{R^bR^c}$, -N$\mathbf{R^bR^c}$, -N$\mathbf{R^c}$C(O)-$\mathbf{R^b}$, -C(O)N$\mathbf{R^bR^c}$, -N$\mathbf{R^c}$S(O_{0-2})$\mathbf{R^b}$, -S(O_{0-2})$\mathbf{R^b}$, wherein $\mathbf{R^b}$ and $\mathbf{R^c}$ are as defined above. Preferably $\mathbf{R^{15}}$ is heterocyclyl. Further preferably $\mathbf{R^{15}}$ is selected from: pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl or thiazolyl. Most preferably $\mathbf{R^{15}}$ is pyridyl.

In a further embodiment of the invention N($\mathbf{R^9R^{10}}$) represent an optionally substituted 3- to 10- membered heterocyclic ring, wherein the optional substituents are selected from $\mathbf{R^{15}}$ as defined above.

Preferably $\mathbf{R^{12}}$ and $\mathbf{R^{12a}}$ are independently selected from: hydrogen, optionally substituted C_{1-6}alkyl or $\mathbf{R^{12}}$ and $\mathbf{R^{12a}}$ together with carbon to which they are attached from an optionally substituted 3- to 6-membered cycloalkyl ring. Further preferably $\mathbf{R^{12}}$ and $\mathbf{R^{12a}}$ are independently selected from: hydrogen, methyl, ethyl or *tert*-butyl. Most preferably $\mathbf{R^{12}}$ and $\mathbf{R^{12a}}$ are both methyl.

Preferably $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$, are independently selected from hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted phenyl and -$\mathbf{R^d}$-phenyl, where $\mathbf{R^d}$ represents C_{1-6}alkylene or and an optionally substituted 3- to 8- membered heterocyclic ring (preferably, a 5- or 6-membered monocyclic ring) containing from 1 to 3 (preferably 1 or 2) further heteroatoms independently selected from O, N and S. Further preferably $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$, are independently selected from hydrogen or C_{1-6}alkyl.

Where optional substitution is mentioned at various places, this refers to one, two, three or more optional substituents. Unless otherwise indicated above (ie, where a list of optional substituents is provided), each substituent can be independently selected from C_{1-8}alkyl (eg, C_{2-6}alkyl, and most preferably methyl, ethyl or *tert*-butyl); C_{3-8}cycloalkoxy, preferably cyclopropoxy, cyclobutoxy or cyclopentoxy; C_{1-6}alkoxy, preferably methoxy or C_{2-4}alkoxy; halo, preferably Cl or F; Hal_3C-, Hal_2CH-, $HalCH_2$-, Hal_3CO-, Hal_2CHO or Hal CH_2O, wherein Hal represents halo (preferably F); $\mathbf{R^g}CH_2O$-, $\mathbf{R^h}$C(O)N(R)-, $\mathbf{R^h}SO_2$N($\mathbf{R}$)- or $\mathbf{R^g}$-$\mathbf{R^h}$N-, wherein $\mathbf{R^g}$ and $\mathbf{R^h}$ independently represent hydrogen or C_{1-8}alkyl (preferably methyl or C_{2-6}alkyl or C_{2-4}alkyl), or $\mathbf{R^g}$-$\mathbf{R^h}$N- represents an optionally substituted C_{3-8}, preferably C_{3-6}, heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; hydrogen; or $\mathbf{R^k}$C(O)O- or $\mathbf{R^k}$C(O)-, $\mathbf{R^k}$ representing hydrogen, optionally substituted phenyl or C_{1-6}alkyl (preferably methyl, ethyl, *iso*-propyl or *tert*-butyl). For optional substitution of the heterocyclic ring represented by $\mathbf{R^g}$-$\mathbf{R^h}$N-, at least one (eg, one, two or three) substituents may be provided independently selected from C_{1-6}alkyl (eg,

C_{2-4}alkyl, more preferably methyl); phenyl; CF_3O-; F_2CHO-; C_{1-8}alkoxy, preferably methoxy, ethoxy or C_{3-6}alkoxy; C_{1-8}alkoxyC(O), preferably methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl or C_{3-6}alkoxyC(O)-; phenoxycarbonyl; phenoxy; C_{1-8}alkanoyl, preferably acetyl, ethanoyl or C_{3-6}alkyanoyl; carboxy; C_{1-8}alkyl$S(O)_{nn}$ wherein **nn** is an integer between 0 and 2, preferably methylthio, ethylthio, C_{3-6}alkylthio, methylsulphinyl, ethylsulphinyl, C_{3-6}alkylsulphinyl, methylsulphonyl, ethylsulphonyl or C_{3-6}alkylsulphonyl; hydroxy; halo (eg, F, Cl or Br); $\mathbf{R^mR^n}$N- where $\mathbf{R^m}$ and $\mathbf{R^n}$ are independently hydrogen or C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl, most preferably $\mathbf{R^m}$=$\mathbf{R^n}$=methyl); and nitro.

Where optional substitution of a ring is mentioned at various places, this most preferably refers to one, two, three or more substituents selected from C_{1-8}alkyl (eg, C_{2-6}alkyl, and most preferably methyl); C_{1-8}alkoxy, preferably methoxy, ethoxy or C_{3-6}alkoxy; C_{1-8}alkyl$S(O)_{nn}$ wherein **nn** is an integer between 0 and 2, preferably methylthio, ethylthio, C_{3-6}alkylthio, methylsulphinyl, ethylsulphinyl, C_{3-6}alkylsulphinyl, methylsulphonyl, ethylsulphonyl or C_{3-6}alkylsulphonyl; halo (eg, F, Cl or Br); cyano; and NO_2.

A preferred group of compounds of the invention comprise compounds of Formula (I) wherein:

$\mathbf{R^{11}}$ is a group of the formula: N($\mathbf{R^9R^{10}}$); and

N($\mathbf{R^9R^{10}}$) represents an optionally-substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S, preferably substituted by heterocyclyl;

or a salt, pro-drug or solvate thereof.

A preferred group of compounds of the invention comprise compounds of Formula (I) wherein:

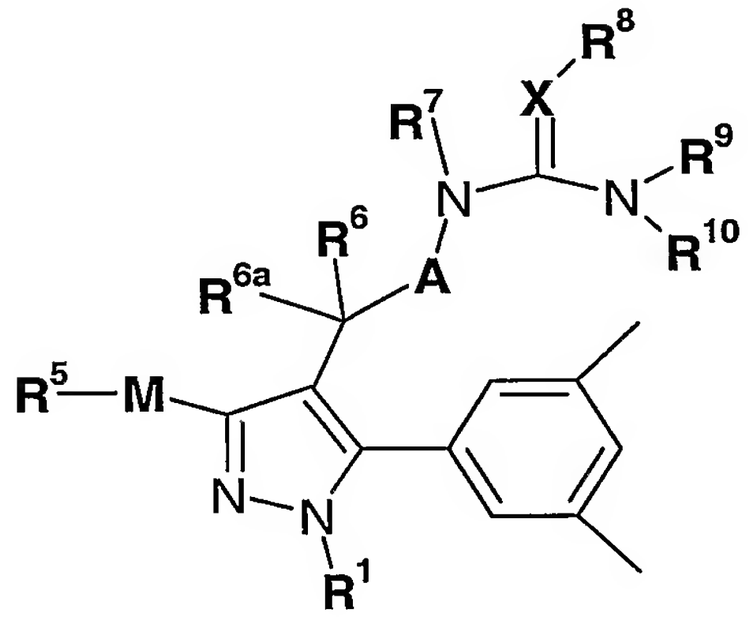
$\mathbf{R^{11}}$ is a group of the formula: N($\mathbf{R^9R^{10}}$);

$\mathbf{R^9}$ is a C_{1-6}alkyl group substituted by an optionally-substituted 3 to 8 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S; and

$\mathbf{R^{10}}$ represents hydrogen or C_{1-6}alkyl

or a salt, pro-drug or solvate thereof.

A preferred group of compounds of the invention comprises a compound of Formula (Ia):



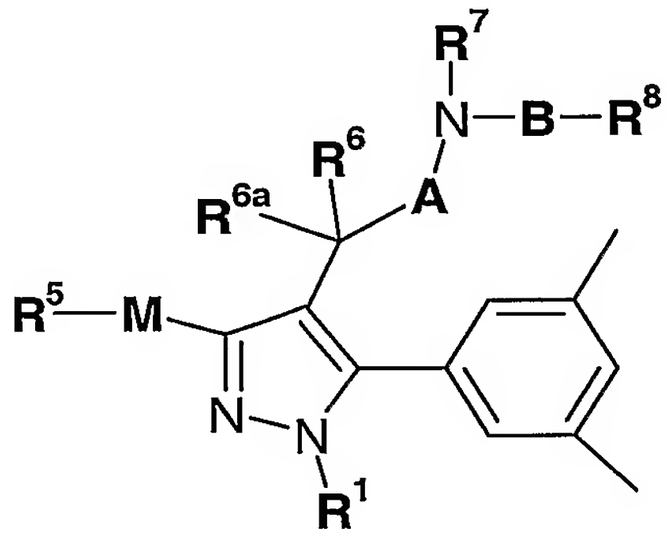
Formula (Ia)

wherein:

A, **B**, **M**, **X**, R^1, R^5, R^6, R^{6a}, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{12a} are as defined above;

or a salt, pro-drug or solvate thereof.

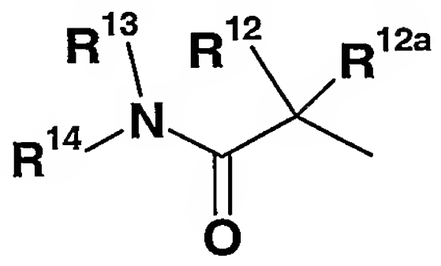
A preferred group of compounds of the invention comprises a compound of Formula (Ib):



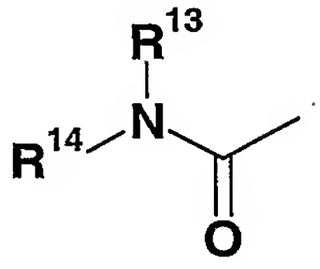
Formula (Ib)

wherein:

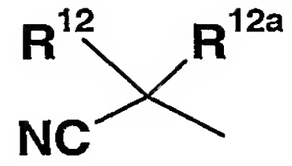
R^5 is selected from: **IIIa**, **IIIb**, **IIIg**, **IIIi** or **IIIj**:



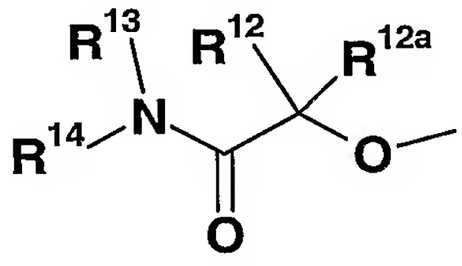
III-a



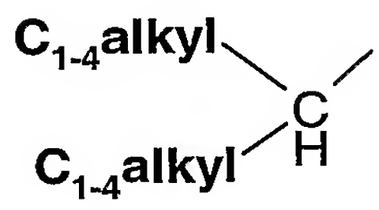
III-b



III-g



III-i

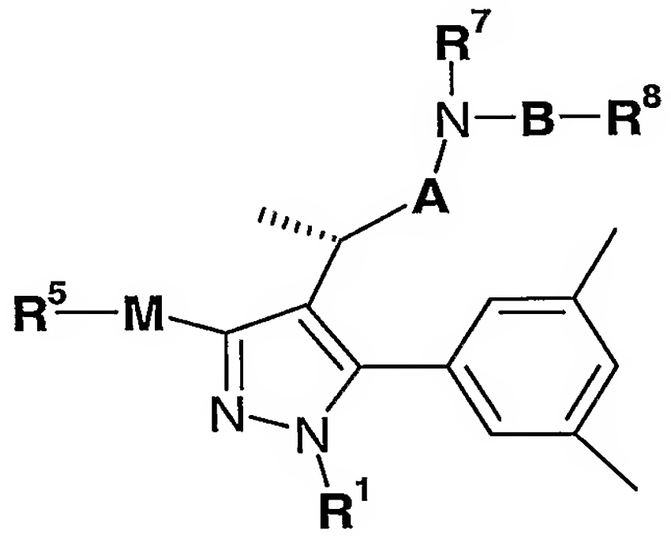


III-j

and **A**, **B**, **M**, **X**, R^1, R^5, R^6, R^{6a}, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{12a}, R^{13}, and R^{14} are as defined above;

or a salt, pro-drug or solvate thereof.

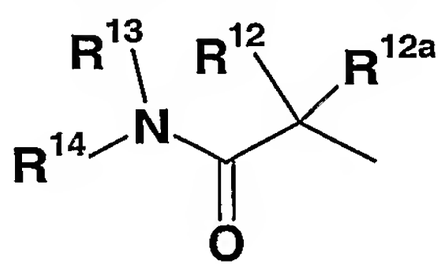
A further preferred group of compounds of the invention comprises a compound of Formula (Ic):



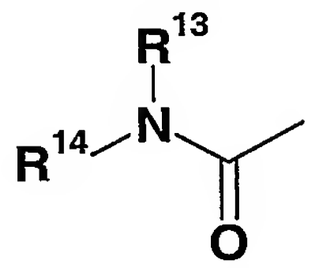
Formula (Ic)

wherein:

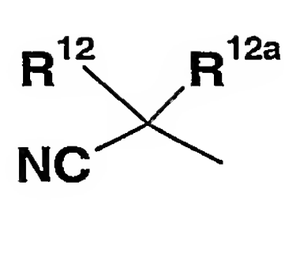
R^5 is selected from a **IIIa**, **IIIb**, **IIIg**, **IIIi** or **IIIj**:



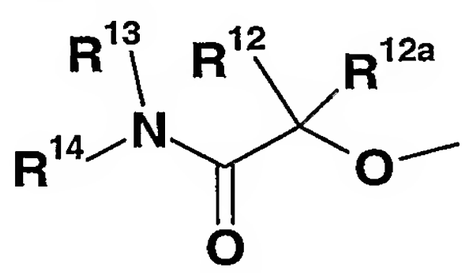
III-a



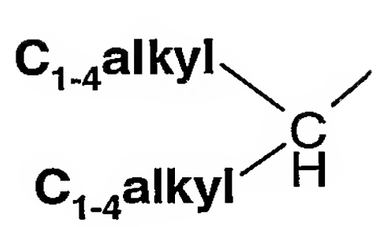
III-b



III-g



III-i



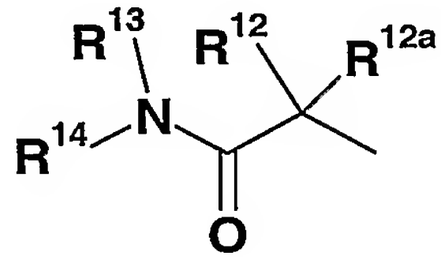
III-j

and **A**, **B**, **M**, **X**, R^1, R^6, R^{6a}, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{12a}, R^{13}, and R^{14} are as defined above;

or a salt, pro-drug or solvate thereof.

A yet further preferred group of compounds of the invention comprises a compound of Formula (Ia), (Ib) or (Ic) wherein:

R^5 is a group of formula **IIIa**:



IIIa ;

$NR^{13}(\text{-}R^{14})$ represents an optionally substituted 7- to 8- membered bicyclic heterocyclic ring and **A**, **B**, **X**, R^1, **M**, R^6, R^{6a}, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{12a} are as defined above;

or a salt, pro-drug or solvate thereof.

A preferred compound according to the present invention is:

3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.1]heptan-7-yl)propyl]-

4-[1S-methyl-2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido) ethyl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole;

or a salt, pro-drug or solvate thereof.

In a further embodiment particularly preferred compounds according to the present invention are wherein the compound is selected from:

isopropyl (1*Z*)-({2-[3-(2,2-dimethyl-3-oxo-3-pyrrolidin-1-ylpropoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]ethyl}amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylidenecarbamate;

isopropyl (1*Z*)-({2-[3-(2,2-dimethyl-3-oxo-3-(7-azabicyclo[2.2.1]hept-7-yl)propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]ethyl}amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylidenecarbamate;

isopropyl (1*Z*)-({2-[3-[3-(diethylamino)-2,2-dimethyl-3-oxopropoxy]-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]ethyl}amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylidenecarbamate;

N-{2-[3-[3-(diethylamino)-2,2-dimethyl-3-oxopropoxy]-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]ethyl}-3-pyridin-4-ylpyrrolidine-1-carboxamide;

or a salt, pro-drug or solvate thereof.

According to a further feature of the first aspect of the invention there is provided a pharmaceutical formulation comprising a compound of Formula (Ia), Formula (Ib), Formula (Ic) or preferred compounds of the invention, or salt, pro-drug or solvate thereof, and a pharmaceutically acceptable diluent or carrier.

According to a further feature of the first aspect of the invention there is provided the following uses of a compound of Formula (Ia), Formula (Ib), Formula (Ic) or preferred compounds of the invention, or salt, pro-drug or solvate thereof:

(a) the use in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity;

(b) the use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinizing hormone by the pituitary gland of the patient; and

(c) the use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient, preferably a sex hormone related condition selected from prostate cancer and pre-menopausal breast cancer.

The compounds of Formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the Formula (I). Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the Formula (I).

Various forms of pro-drugs are known in the art. For examples of such pro-drug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of the Formula (I) containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters.

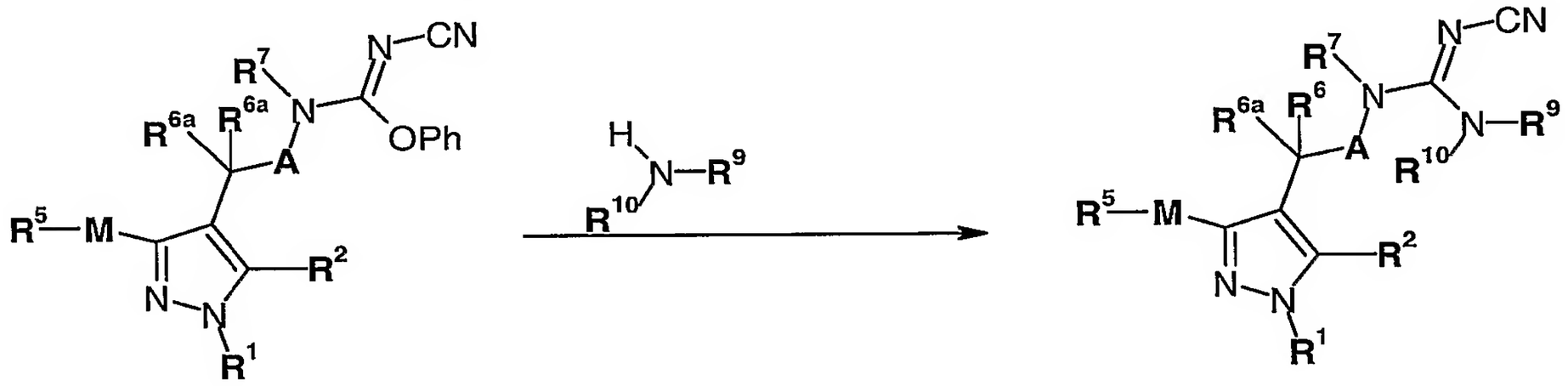
An in-vivo hydrolysable ester of a compound of the Formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a compound of the invention which is

sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

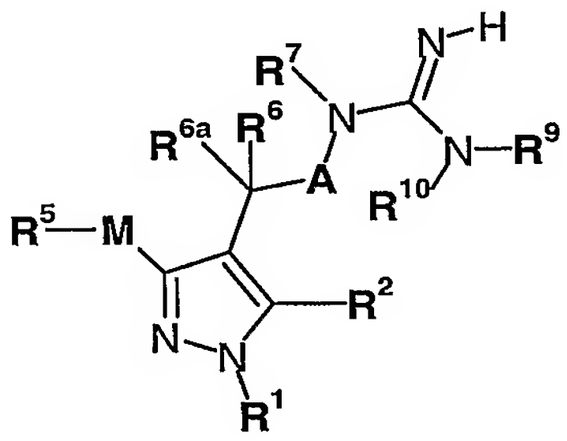
The compounds of Formula (I) can be prepared by a process comprising a step selected from (a) to (f) as follows, these processes are provided as a further feature of the invention:-

(a) for compounds wherein **X** is N and $\mathbf{R^8}$ is CN, reaction of a compound of formula **XXXII** as follows



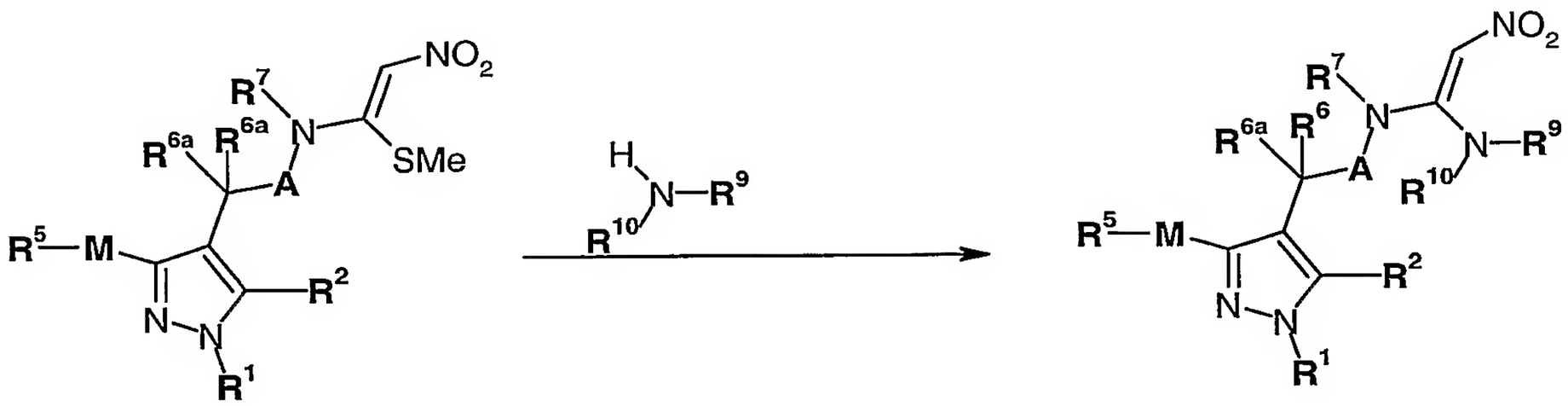
XXXII **XXXIII**

(b) for compounds wherein **X** is N and $\mathbf{R^8}$ is hydrogen, cleavage of the cyano group of compound of formula **XXXIII** in the presence of acid to produce compound of formula **XXXIV**



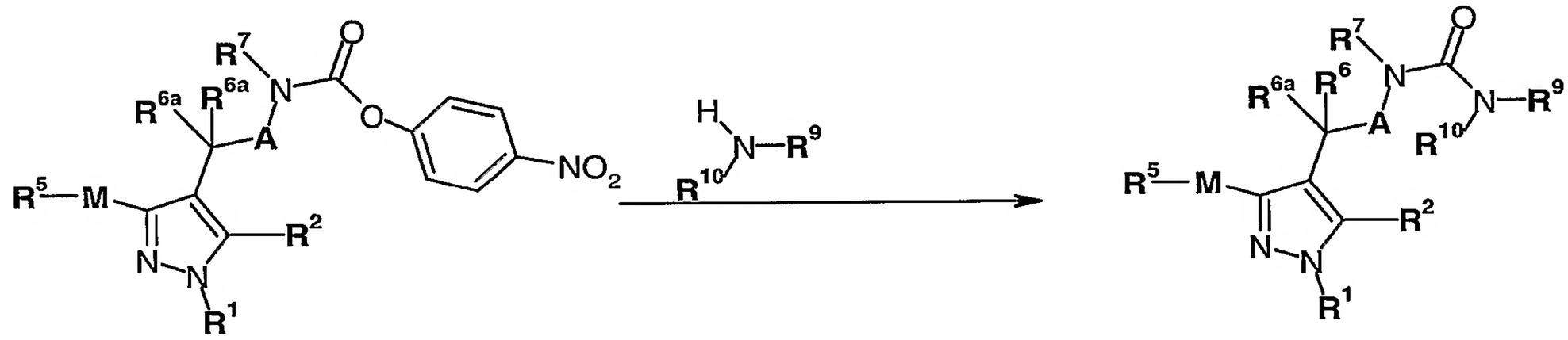
XXXIV

(c) for compounds wherein **X** is CH and $\mathbf{R^8}$ is NO_2, reaction of compound of formula **XXXV** as follows



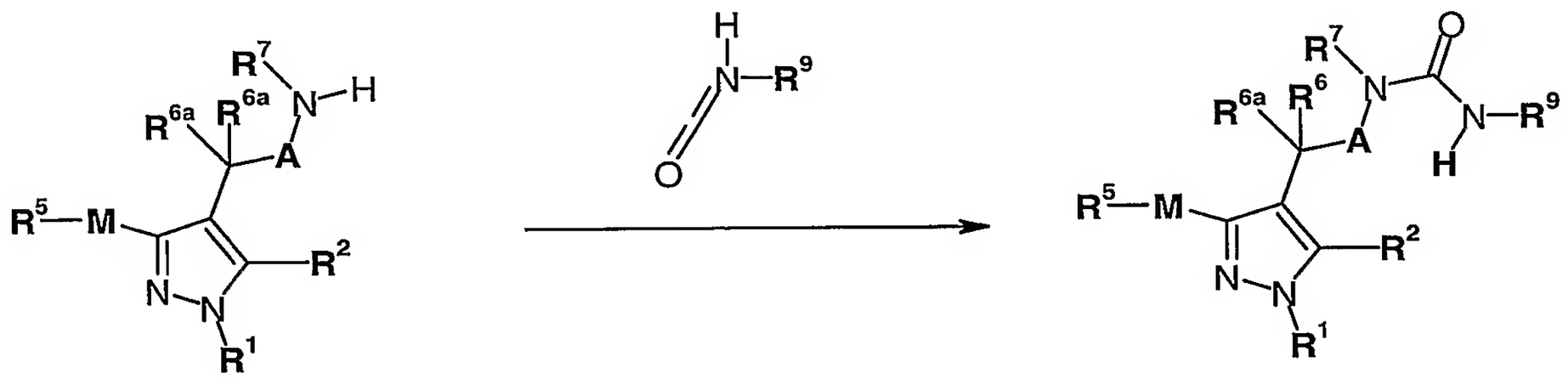
XXXV XXXVI

(d) for compounds where **X-R^8** is O, reaction of compound of formula **XXXVII** as follows



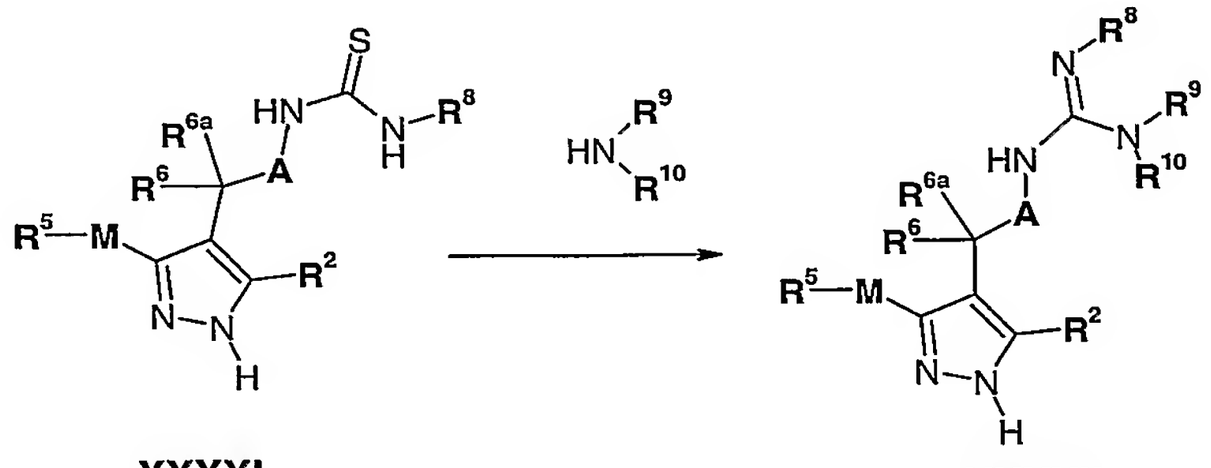
XXXVII XXXVIII

(e) for compounds where **X-R^8** is O, reaction of compound of formula **XXXIX** as follows



XXXIX XXXX

(f) to form a compound wherein **X** is nitrogen and Reaction of a compound of formula XXXXI as follows



XXXXI XXXXII

and thereafter if necessary:

i) converting a compound of the Formula (I) into another compound of the Formula (I);

ii) removing any protecting groups;

iii) forming a salt, pro-drug or solvate.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of Formula (I) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and de-protection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The de-protection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

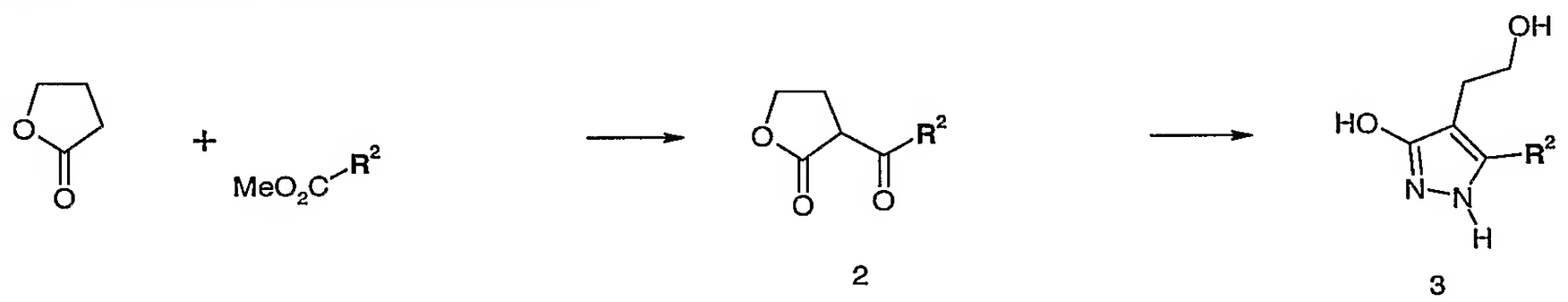
A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The de-protection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with

a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

EXPERIMENTAL

GENERAL REACTION SCHEMES

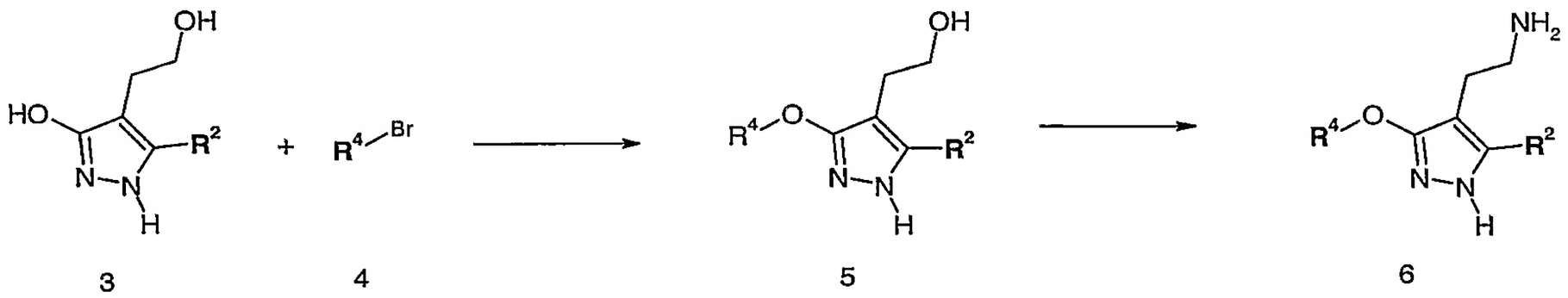


Scheme a

Pyrazoles, such as **3** can be synthesised in two steps (Scheme a):

(1) by the reaction of a lactone with the appropriate ester using a Claisen condensation to form a compound of formula **2**, under conditions of an inert atmosphere, such as argon, at a temperature of about 0°C in a suitable solvent such as THF.

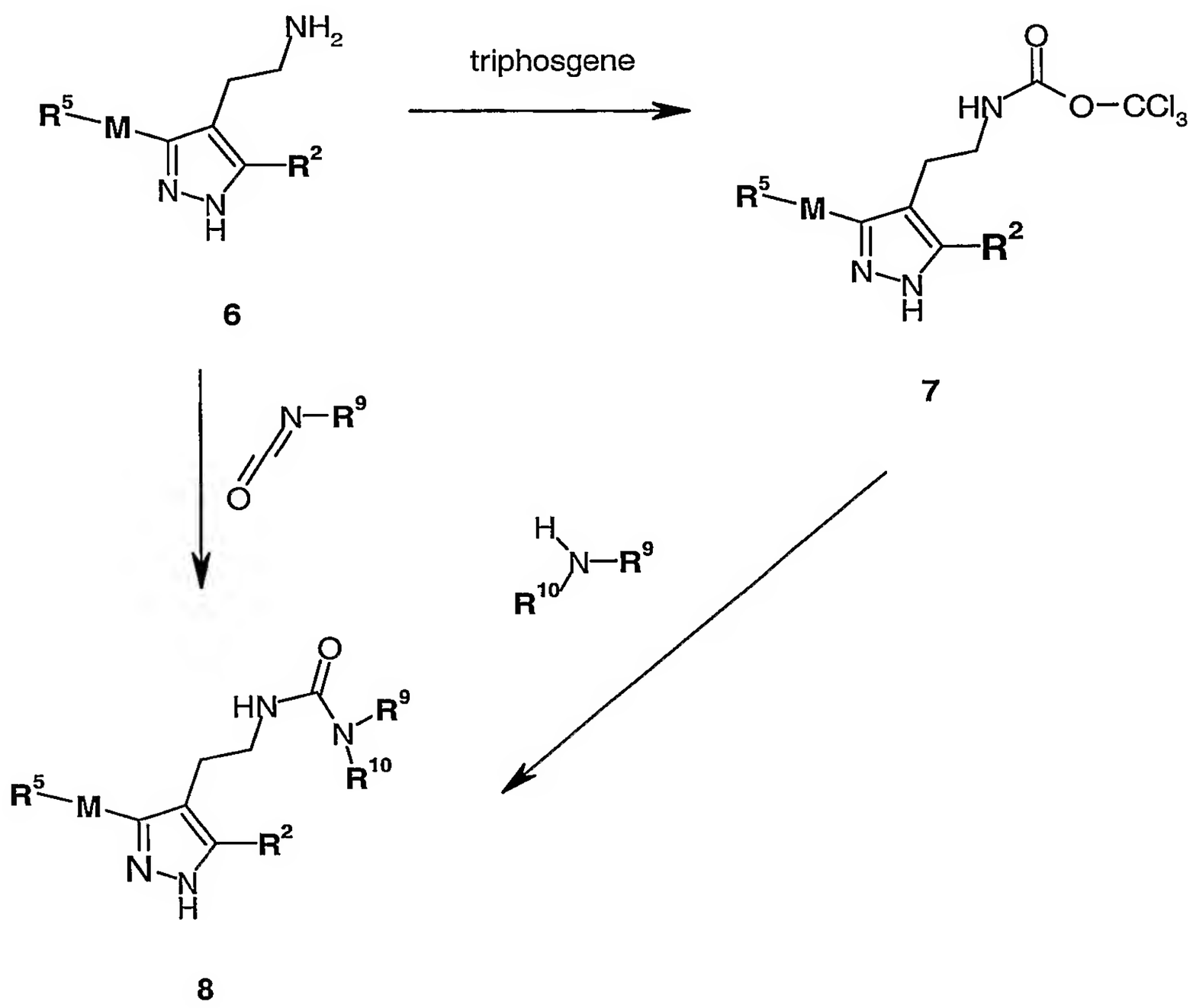
(2) followed by cyclization of a compound of formula **2** with hydrazine to form the pyrazole **3**, at a room temperature in a suitable solvent such as ethanol.



Scheme b

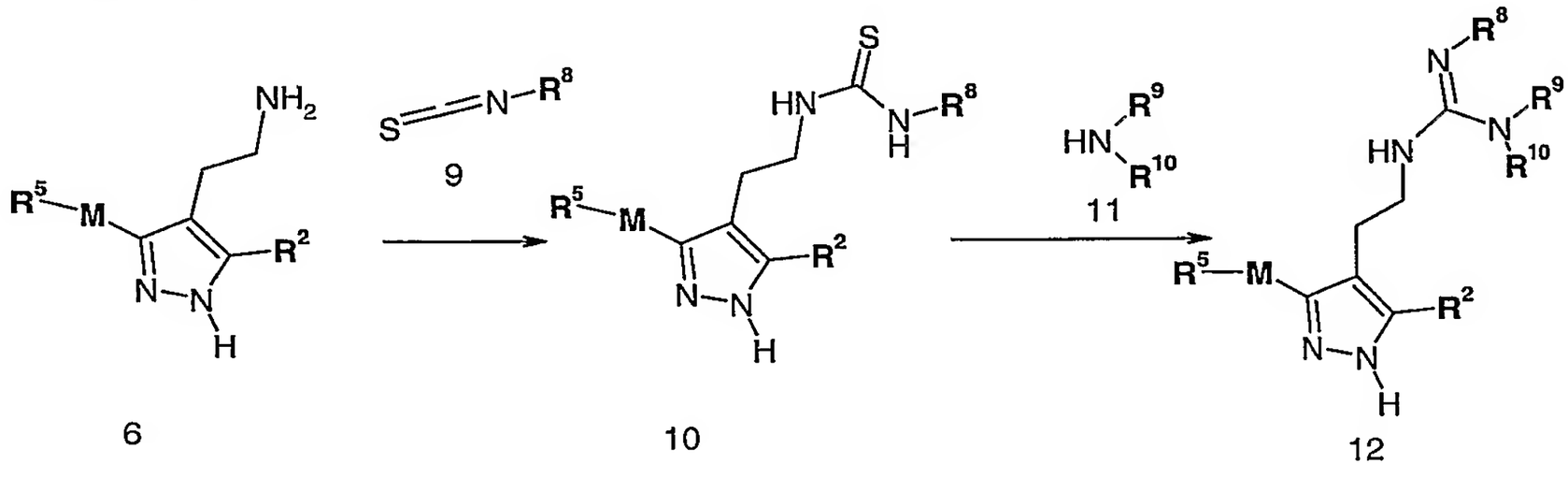
The pyrazole **3** can undergo a selective alkylation reaction with a compound of formula **4**, under conditions of an inert atmosphere, such as argon, in the presence of a suitable base, such as potassium carbonate in the a suitable solvent such as DMA at a temperature of about 90°C, to form a compound of formula **5**. Then the amine **6** can be

prepared from a compound of formula **5** and phthalimide using a Mitsunobu reaction with an activating agent such as diethyldiazocarboxylate (DEAD), diisopropyldiazocarboxylate or the like with triphenylphosphine, tri-butylphosphine and the like, in an inert solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof, followed by deprotection with hydrazine (Scheme b).



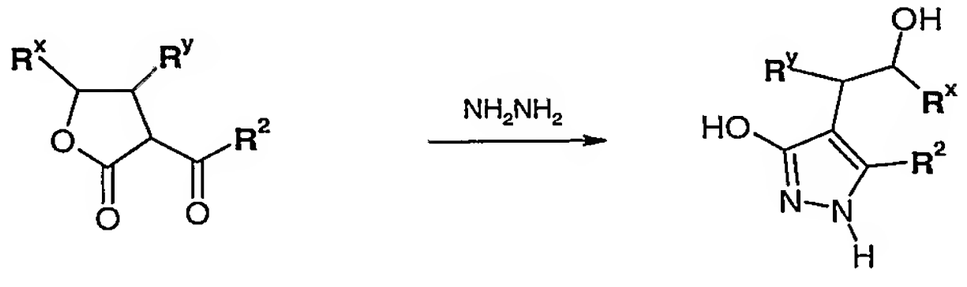
Scheme c.

A suitable pyrazole **6** can be converted to a urea by either direct treatment with an iso-cyanate in an inert solvent such as methylene chloride, chloroform or THF and the such like, or by a two step procedure of reaction with triphosgene (**6**→**7**) followed by addition of an amine (**7**→**8**), bearing the required substitution to yield **8** (Scheme c).



A suitable pyrazole (**6**) can be converted to a guandine or guanidine derivative (**12**) by reaction with a suitable isothiocyanate (**9**) to form a compound of formula **10**, followed by displacement by a suitable amine (**11**) (Scheme d).

Thus, according to a further feature of the invention there is provided a process for the synthesis of a substituted pyrazole of formula XXXXIV which comprises reaction of a compound of formula XXXXIII with hydrazine.



XXXXIII XXXXIV

wherein:

R^2 is as defined above; and

R^x and R^y are independently selected from: optionally substituted alkyl, optionally substituted aryl or optionally substituted heteocyclyl.

According to a further feature of the invention there is provided an intermediate compound of formula XXXXIII as defined above.

EXAMPLES

The invention will now be illustrated with the following non-limiting Examples in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in *vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

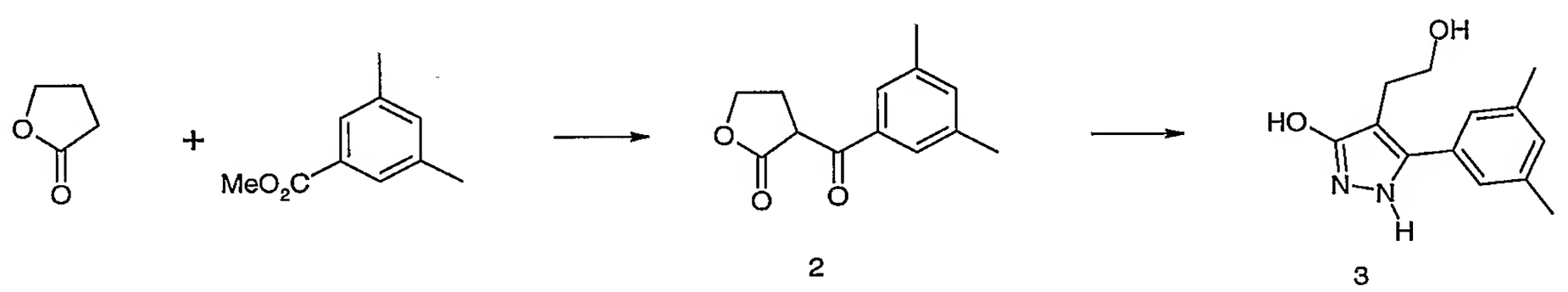
(vi) chromatography was performed on silica (Merck Keiselgel: Art.9385);

Abbreviations

DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate
DMSO	dimethyl sulphoxide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DNS	2,4-dinitrobenzenesulphonyl
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBt	1-hydroxybenotriazole
LHMDS	lithium bis(trimethylsilyl)amide
THF	tetrahydrofuran

Starting Materials

The starting material were prepared as follows:-



A solution of methyl 3,5-dimethylbenzoate (25 g ; 152 mmol) and butyrolactone (40 ml ; 520 mmol) in THF (300 ml) under argon was cooled to 0°C and treated dropwise with LHMDS (200 ml ; 200 mmol ; 1M in hexanes). The mixture was stirred and allowed to warm to room

temperature overnight. The THF was evaporated. The residue was taken up in Et_2O and the organic phase was washed with sat. aq. $NaHCO_3$, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (20 to 40% EtOAc) to give an oil which slowly crystallised to give **2** as a white solid (9.2 g). During the chromatography, the starting material methyl 3,5-dimethylbenzoate (12.4g) was recovered.

Yield : 55% based on recovered methyl 3,5-dimethylbenzoate.

^1H NMR spectrum ($CDCl_3$) : 2.39 (s, 6H) ; 2.5 (m, 1H) ; 2.82 (m, 1H) ; 4.41 (m, 1H) ; 4.51 (m, 2H) ; 7.25 (s, 1H) ; 7.65 (s, 2H).

MS-ESI : 219 $[M+H]^+$

Compound **2** (7.43 g ; 34 mmol) was dissolved in EtOH (200 ml) and hydrazine hydrate (17.2 ml ; 354 mmol) was added. The mixture was stirred for 30 min. The solvent was evaporated and the residue was triturated with pentane to give **3** as a white solid (7.05 g).

Yield : 90%

^1H NMR spectrum (DMSO d_6) : 2.32 (s, 6H) ; 2.58 (t, 2H) ; 3.50 (t, 2H) ; 4.8 (br s, 1H) ; 7.01 (s, 1H) ; 7.14 (s, 2H) ; 9.5 (br s, 1H).

MS-ESI : 233 $[M+H]^+$

A mixture of **3** (4.26 g ; 18.4 mmol) and **4** (4.51 g ; 19.3 mmol) in DMA (40 ml) under argon was treated with K_2CO_3 (5.07 g ; 36.7 mmol). The mixture was stirred and heated at 90°C for 2h. The mixture was poured into sat. aq. $NaHCO_3$, extracted with EtOAc and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 100% EtOAc) to give the alcohol **5** as a pale yellow oil (6.56 g).

Yield : 93%

^1H NMR spectrum (DMSO d_6) : 1.30 (s, 6H) ; 1.8 (m, 4H) ; 2.33 (s, 6H) ; 2.55 (m, 2H) ; 3.32 (m, 2H) ; 3.5 (m, 4H) ; 4.17 (s, 2H) ; 4.62 (t, 1H) ; 7.04 (s, 1H) ; 7.16 (s, 2H) ; 11.9 (br s, 1H).

MS-ESI : 386 $[M+H]^+$

A mixture of **5** (3.85 g ; 10 mmol), phthalimide (1.62 g ; 11 mmol) and triphenylphosphine (10.5 g ; 40 mmol) in THF (100 ml) at 0°C under argon was treated with DEAD (6.33 ml ; 40 mmol). The mixture was stirred at this temperature for 1h when water was added. The mixture was extracted with Et_2O and the organic phase was washed with water, brine and dried over $MgSO_4$.

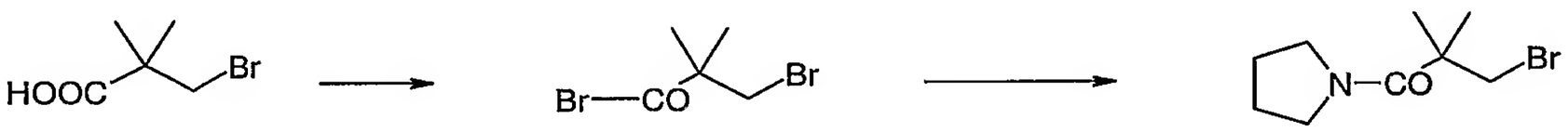
Evaporation gave a crude solid which, without further purification, was immediately taken up in EtOH (50 ml) and treated with hydrazine hydrate (5 ml ; 100 mmol). The mixture was stirred for 1.5h and then the EtOH was partially evaporated. Addition of CH_2Cl_2 caused precipitation of phthalhydrazide which was filtered and rinsed with CH_2Cl_2. The filtrate was evaporated and the residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 8% MeOH) to give **6** as a beige solid (2.34 g).

Yield : 61%

^{1}H NMR spectrum (DMSO d_6) : 1.30 (s, 6H) ; 1.79 (m, 4H) ; 2.33 (s, 6H) ; 2.52 (m, 2H) ; 2.67 (t, 2H) ; 3.5 (m, 4H) ; 4.18 (s, 2H) ; 7.03 (s, 1H) ; 7.14 (s, 2H) ; 8.95 (br s, 1H).

MS-ESI : 385 $[M+H]^+$

Starting material **4** was prepared as follows:-



8 9 4

A mixture of **8** (14.48 g ; 80 mmol) and oxalyl bromide (43.2 g ; 200 mmol) containing one drop of DMF was heated at 50°C for 2h and then cooled. The excess of oxalyl bromide was evaporated and the residue azeotroped with toluene to give crude **9** which was taken up directly in CH_2Cl_2 (25 ml) and cooled to 0°C. Diisopropylethylamine (14 ml ; 80 mmol) was added followed by a solution of pyrrolidine (3.3 ml ; 40 mmol) in CH_2Cl_2 (30 ml). The mixture was allowed to warm to room temperature overnight and was diluted with CH_2Cl_2, washed with aq. HCl (2N), aq. NaOH (1N), water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH2Cl2 (5 to 10% EtOAc) to give **4** as a white solid (6.5 g).

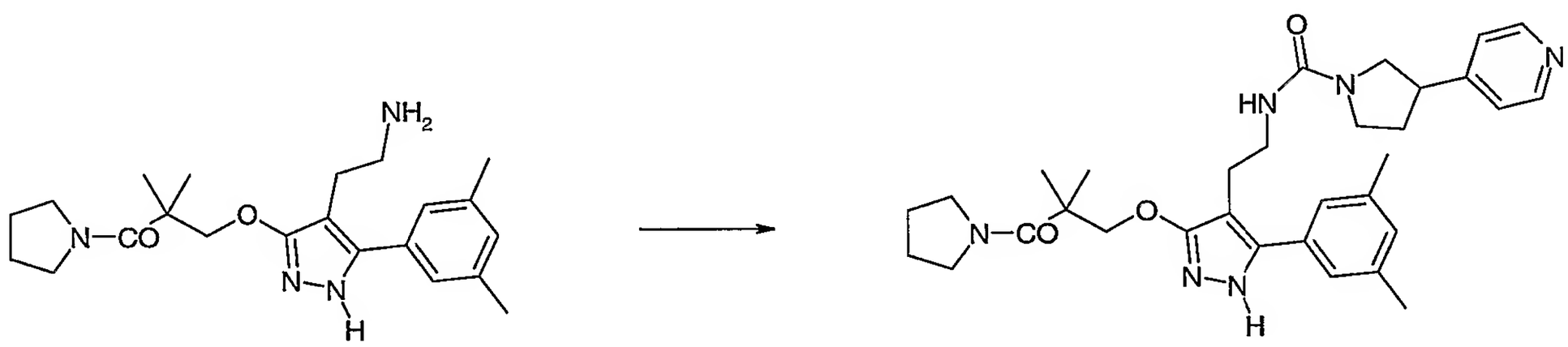
Yield : 70%

^{1}H NMR spectrum (DMSO d_6) : 1.39 (s, 6H) ; 1.9 (m, 4H) ; 3.57 (m, 4H) ; 3.62 (s, 2H)

MS-ESI : 235 $[M+H]^+$

Example 1

3-[2,2-dimethyl-3-oxo-3-(pyrrolidin-1-yl)propoxy]-4-[2-(3-pyridin-4-ylpyrrolidin-1-carboxamido)ethyl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole



Example 1

6

A solution of **6** (150 mg ; 0.39 mmol) in CH_2Cl_2 (2 ml) was cooled to 0°C. Diisopropylethylamine (136 ul ; 0.78 mmol) was added followed by a solution of 4-nitrophenyl chloroformate (83 mg ; 0.41 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred for 3h when a solution of 4-(3-pyrrolidyl)-pyridine (70 mg ; 0.47 mmol) in CH_2Cl_2 (2 ml) was added and the mixture was allowed to warm to room temperature overnight. The mixture was directly purified by flash chromatography eluting with increasingly polar mixtures of MeOH/EtOAc (0 to 10% MeOH) to give **Example 1** as a beige solid (95 mg).

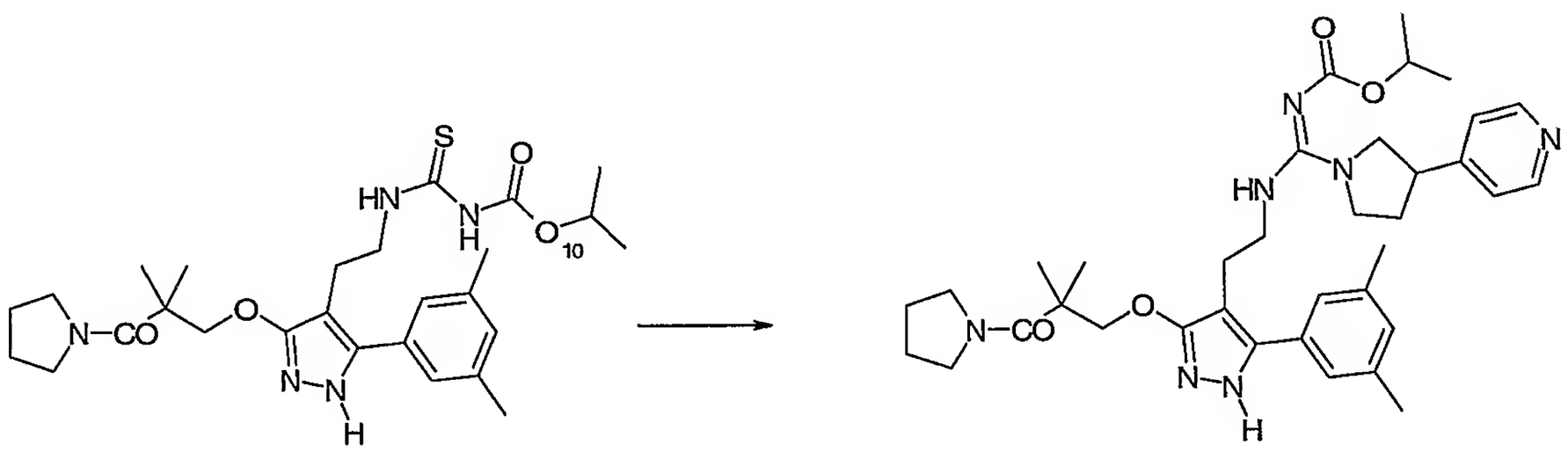
Yield : 44%

^{1}H NMR spectrum (DMSO d_6) : 1.29 (s, 6H) ; 1.75 (m, 4H) ; 1.95 (m, 1H) ; 2.2 (m, 1H) ; 2.31 (s, 6H) ; 2.56 (m, 2H) ; 3.1-3.4 (m, 6H) ; 3.5 (m, 4H) ; 3.64 (m, 1H) ; 4.18 (s, 2H) ; 6.22 (t, 1H) ; 6.99 (s, 1H) ; 7.21 (s, 2H) ; 7.27 (d, 2H) ; 8.48 (d, 2H).

MS-ESI : 559 $[M+H]^+$

Example 2

3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.1]heptan-7-yl)propyl]-4-[2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido)ethyl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole



Example 2

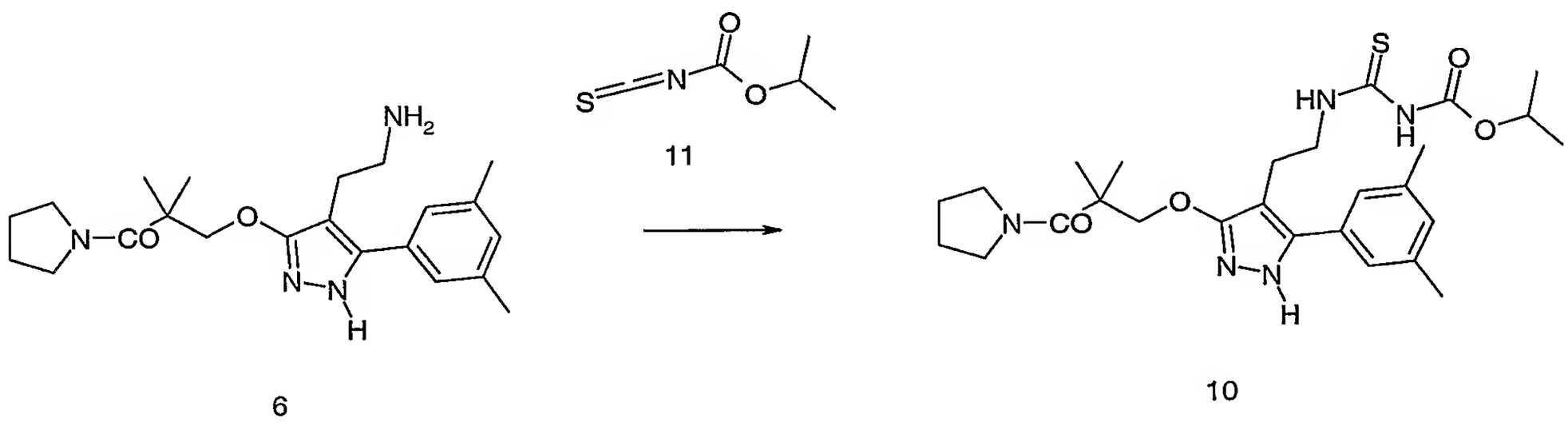
A solution of **10** (260 mg ; 0.5 mmol) in CH_2Cl_2 (5 ml) was cooled to 0°C. EDCI (145 mg ; 0.75 mmol) and diisopropylethylamine (130 ul ; 0.75 mmol) were added followed by 4-(3-pyrrolidyl)-pyridine (111 mg ; 0.75 mmol) and the mixture was allowed to warm to room temperature overnight. The mixture was diluted with CH_2Cl_2 and the organic phase was washed with sat. aq. $NaHCO_3$, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 100% EtOAc) to give **Example 2** as a beige solid (277 mg).

Yield : 86%

^{1}H NMR spectrum (DMSO d_6) : 1.07 (m, 6H) ;1.29 (s, 6H) ; 1.8 (m, 4H) ; 1.95 (m, 1H) ; 2.2 (m, 1H) ; 2.30 (s, 6H) ; 2.65 (m, 2H) ; 3.2-3.4 (m, 6H) ; 3.5 (m, 4H) ; 3.65 (m, 1H) ; 4.18 (s, 2H) ; 4.6 (m, 1H) ; 6.95 (m,1H) ; 7.00 (s, 1H) ; 7.12 (s, 2H) ; 7.27 (d, 2H) ; 8.49 (d, 2H).

MS-ESI : 644 $[M+H]^+$

The starting material **10** was prepared as follows:-



6 11 10

A solution of **6** (200 mg ; 0.52 mmol) in CH_2Cl_2 (2 ml) was cooled to 0°C. A solution of **11** (115 mg ; 0.78 mmol) was added and the mixture was allowed to warm to room temperature for 1h. The mixture was treated with water, diluted with CH_2Cl_2 and the organic phase was washed with brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of Et_2O/hexanes (0 to 100% Et_2O) to give **10** as a beige solid (260 mg).

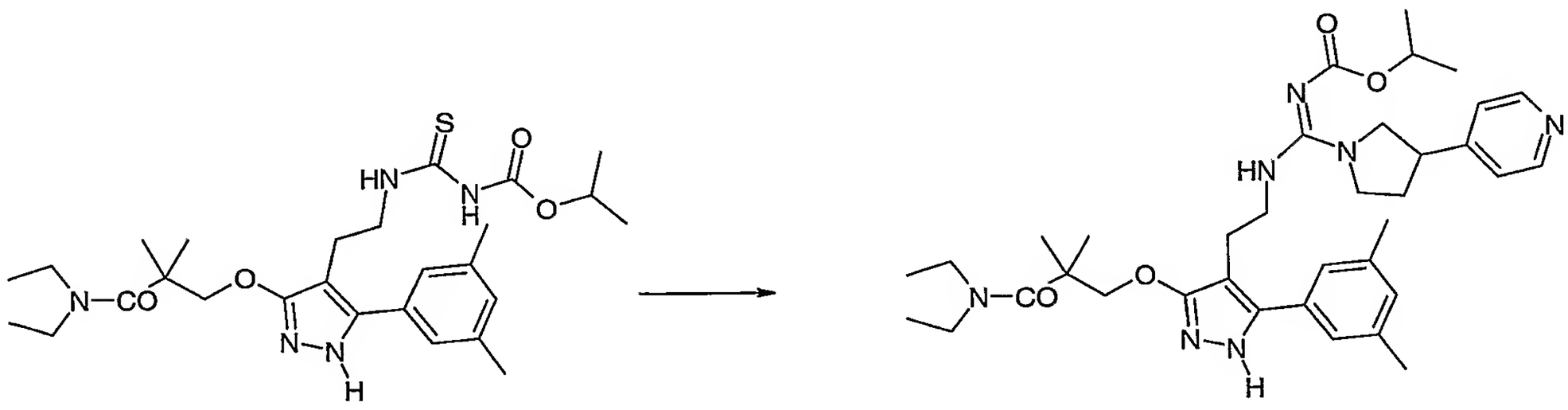
Yield : 94%

^1H NMR spectrum (DMSO d_6) : 1.22 (m, 6H) ;1.31 (s, 6H) ; 1.8 (m, 4H) ; 2.32 (s, 6H) ; 2.71 (m, 2H) ; 3.5 (m, 4H) ; 3.74 (m, 2H) ; 4.20 (s, 2H) ; 4.83 (m, 1H) ; 7.02 (s,1H) ; 7.17 (s, 2H) ; 9.89 (t, 1H) ; 10.81 (s, 1H).

MS-ESI : 530 $[M+H]^+$

Example 3

3-[2,2-dimethyl-3-oxo-3-(N,N-diethylamino)propyl]-4-[2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido)ethyl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole



Bb4 Example 3

A solution of **Bb4** (156 mg ; 0.29 mmol) in CH_2Cl_2 (2 ml) was cooled to 0°C. EDCI (85 mg ;

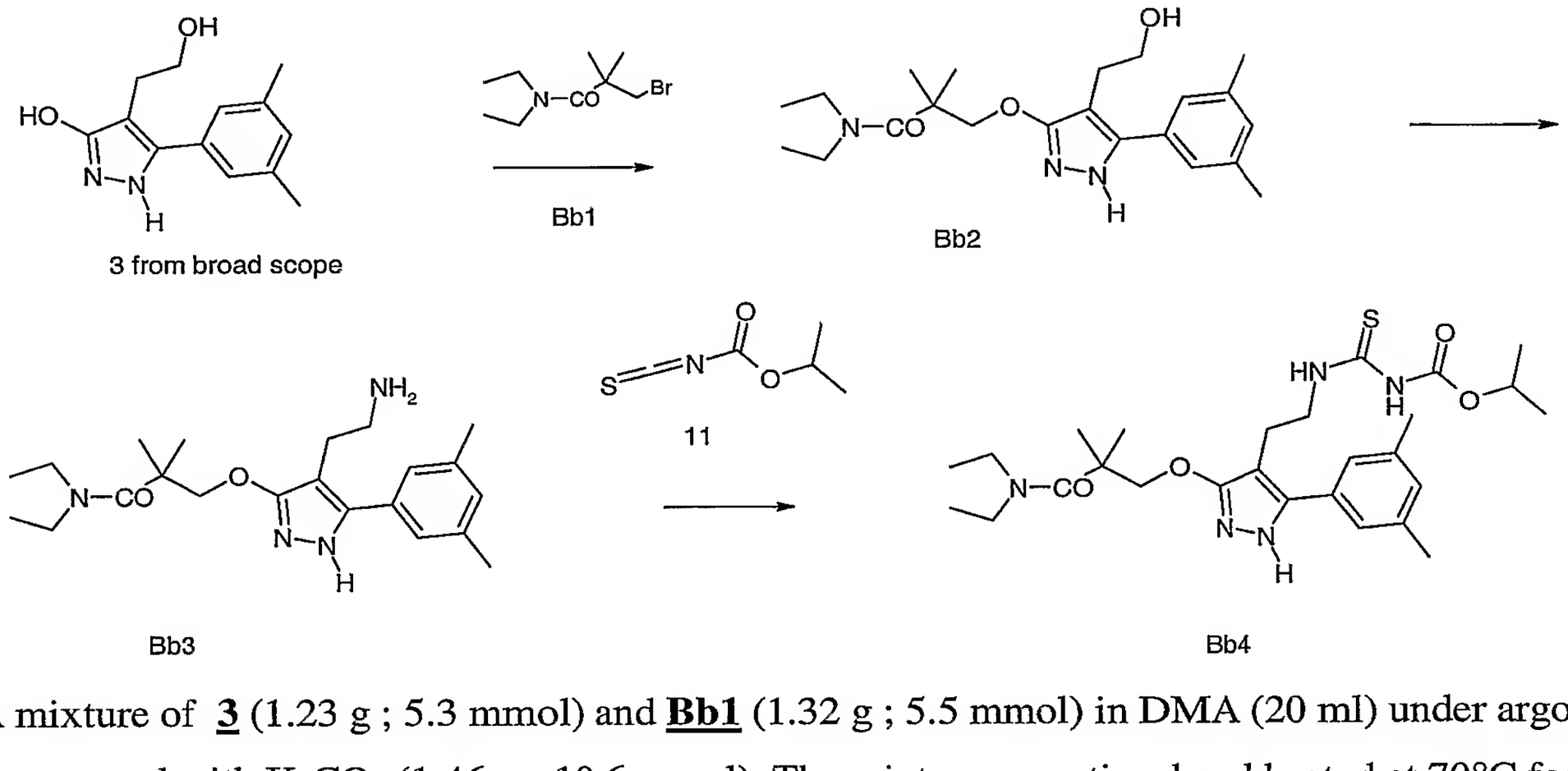
0.44 mmol) and diisopropylethylamine (77 ul ; 0.44 mmol) were added followed by 4-(3-pyrrolidyl)-pyridine (56 mg ; 0.38 mmol) and the mixture was allowed to warm to room temperature overnight. The mixture was diluted with CH_2Cl_2 and the organic phase was washed with sat. aq. $NaHCO_3$, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of MeOH/CH_2Cl_2 (0 to 100% MeOH) to give **Example 3** as a beige solid (180 mg).

Yield : 96%

^{1}H NMR spectrum (DMSO d_6) : 1.07 (m, 12H) ;1.31 (s, 6H) ; 1.93 (m, 1H) ; 2.23 (m, 1H) ; 2.30 (s, 6H) ; 2.65 (m, 2H) ; 3.2-3.55 (m, 10H) ; 3.57 (m, 1H) ; 4.17 (s, 2H) ; 4.58 (m, 1H) ; 6.95 (m,1H) ; 7.00 (s, 1H) ; 7.13 (s, 2H) ; 7.27 (d, 2H) ; 8.50 (d, 2H) ;11.9 (br s, 1H).

MS-ESI : 646 $[M+H]^+$

The starting material **Bb4** was prepared as follows:-



A mixture of **3** (1.23 g ; 5.3 mmol) and **Bb1** (1.32 g ; 5.5 mmol) in DMA (20 ml) under argon was treated with K_2CO_3 (1.46 g ; 10.6 mmol). The mixture was stirred and heated at 70°C for 2h. The mixture was poured into sat. aq. $NaHCO_3$, extracted with EtOAc and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 100% EtOAc) to give the alcohol **Bb2** as a pale yellow oil (1.92 g).

Yield : 94%

^{1}H NMR spectrum (DMSO d_6) : 1.08 (t, 6H) ; 1.32 (s, 6H) ; 2.33 (s, 6H) ; 2.57 (m, 2H) ; 3.38 (m, 4H) ; 3.5 (m, 1H) ; 4.18 (s, 2H) ; 4.61 (t, 1H) ; 7.04 (s, 1H) ; 7.16 (s, 2H) ; 11.9 (br s, 1H).

MS-ESI : 388 $[M+H]^+$

A mixture of **Bb2** (1.92 g ; 4.96 mmol), phthalimide (0.8 g ; 5.46 mmol) and triphenylphosphine (5.24 g ; 20 mmol) in THF (50 ml) at 0°C under argon was treated with DEAD (3.2 ml ; 20 mmol). The mixture was stirred at this temperature for 2h when water was added. The mixture was extracted with Et_2O and the organic phase was washed with water, brine and dried over $MgSO_4$.

Evaporation gave a crude solid which, without further purification, was immediately taken up in EtOH (50 ml) and treated with hydrazine hydrate (2.5 ml ; 50 mmol). The mixture was stirred for 2h and then the EtOH was partially evaporated. Addition of CH_2Cl_2 caused precipitation of phthalhydrazide which was filtered and rinsed with CH_2Cl_2. The filtrate was evaporated and the residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 100% EtOAc) to give **Bb3** as a beige solid (0.865 g).

Yield : 45%

^{1}H NMR spectrum (DMSO d_6) : 1.06 (t, 6H) ; 1.30 (s, 6H) ; 2.32 (s, 6H) ; 2.47 (m, 2H) ; 2.66 (t, 2H) ; 3.35 (m, 4H) ; 4.16 (s, 2H) ; 7.02 (s, 1H) ; 7.13 (s, 2H) ; 11.9 (br s, 1H).

MS-ESI : 387 $[M+H]^+$

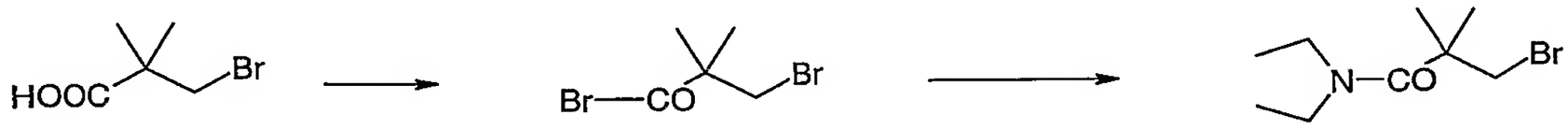
A solution of **Bb3** (210 mg ; 0.544 mmol) in CH_2Cl_2 (5 ml) was cooled to 0°C. A solution of **11** (120 mg ; 0.82 mmol) was added and the mixture was allowed to warm to room temperature for 1h. The mixture was treated with water, diluted with CH_2Cl_2 and the organic phase was washed with brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with CH_2Cl_2 to give **Bb4** as a beige solid (235 mg).

Yield : 81%

^{1}H NMR spectrum ($CDCl_3$) : 1.18 (t, 6H) ; 1.27 (d, 6H) ;1.44 (s, 6H) ; 2.38 (s, 6H) ; 2.87 (m, 2H) ; 3.45 (m, 4H) ; 3.88 (m, 2H) ; 4.36 (s, 2H) ; 4.93 (m, 1H) ; 7.04 (s,1H) ; 7.11 (s, 2H) ; 7.81 (s, 1H) ; 8.9 (s br, 1H) ; 9.7 (s, 1H).

MS-ESI : 532 $[M+H]^+$

Starting material **Bb1** was prepared as follows:-



8 9 Bb1

A mixture of **8** (14.48 g ; 80 mmol) and oxalyl bromide (43.2 g ; 200 mmol) containing one drop of DMF was heated at 50°C for 2h and then cooled. The excess of oxalyl bromide was evaporated and the residue azeotroped with toluene to give crude **9** which was taken up directly in CH_2Cl_2 (25 ml) and cooled to 0°C. Diisopropylethylamine (14 ml ; 80 mmol) was added followed by a solution of pyrrolidine (3.3 ml ; 40 mmol) in CH_2Cl_2 (30 ml). The mixture was allowed to warm to room temperature overnight and was diluted with CH_2Cl_2, washed with aq. HCl (2N), aq. NaOH (1N), water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (5 to 10% EtOAc) to give **Bb1** as a white solid (6.5 g).

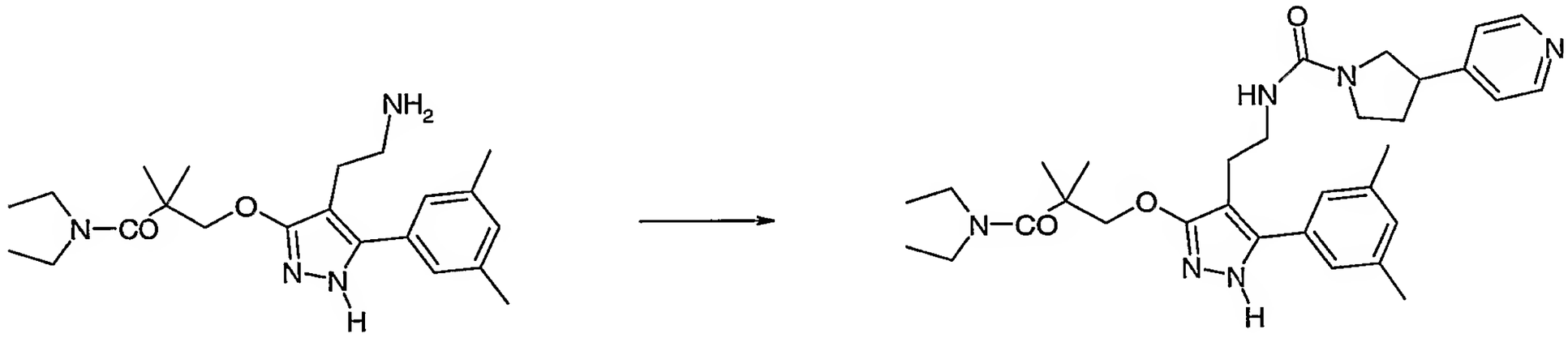
Yield : 70%

^{1}H NMR spectrum (DMSO d_6) : 1.19 (m, 6H) ; 1.42 (s, 6H) ; 3.41 (m, 4H) ; 3.65 (s, 2H)

MS-ESI : 237 $[M+H]^+$

Example 4

3-[2,2-dimethyl-3-oxo-3-(N,N-diethylamino)propyl]-4-[2-(3-pyridin-4-ylpyrrolidin-1-carboxamido)ethyl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole



Bb3 Example 4

A solution of **Bb3** (150 mg ; 0.39 mmol) in CH_2Cl_2 (2 ml) was cooled to 0°C. Diisopropylethylamine (135 ul ; 0.78 mmol) was added followed by a solution of 4-nitrophenyl chloroformate (83 mg ; 0.41 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred for 3h when a solution of 4-(3-pyrrolidyl)-pyridine (70 mg ; 0.47 mmol) in CH_2Cl_2 (2 ml) was added and the mixture was allowed to warm to room temperature overnight. The mixture was directly purified by flash chromatography eluting with increasingly polar mixtures of MeOH/EtOAc (0 to 10% MeOH) to give **Example 4** as a beige solid (138 mg).

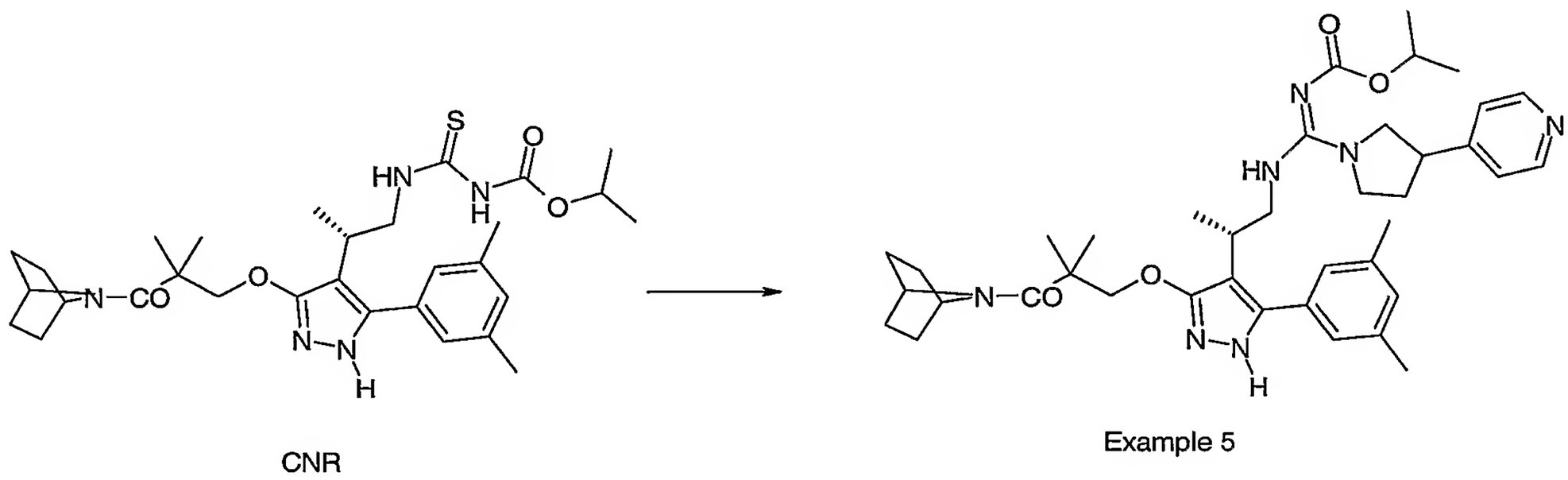
Yield : 63%

^{1}H NMR spectrum (DMSO d_6) : 1.05 ; (m, 6H) ; 1.32 (s, 6H) ; 1.89 (m, 1H) ; 2.2 (m, 1H) ; 2.31 (s, 6H) ; 2.57 (m, 2H) ; 3.1-3.4 (m, 10H) ; 3.64 (m, 1H) ; 4.17 (s, 2H) ; 6.22 (t, 1H) ; 6.99 (s, 1H) ; 7.22 (s, 2H) ; 7.27 (d, 2H) ; 8.48 (d, 2H) ; 11.9 (br s, 1H).

MS-ESI : 561 $[M+H]^+$

Example 5

3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.1]heptan-7-yl)propyl]-4-[1S-methyl-2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido) ethyl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole



CNR Example 5

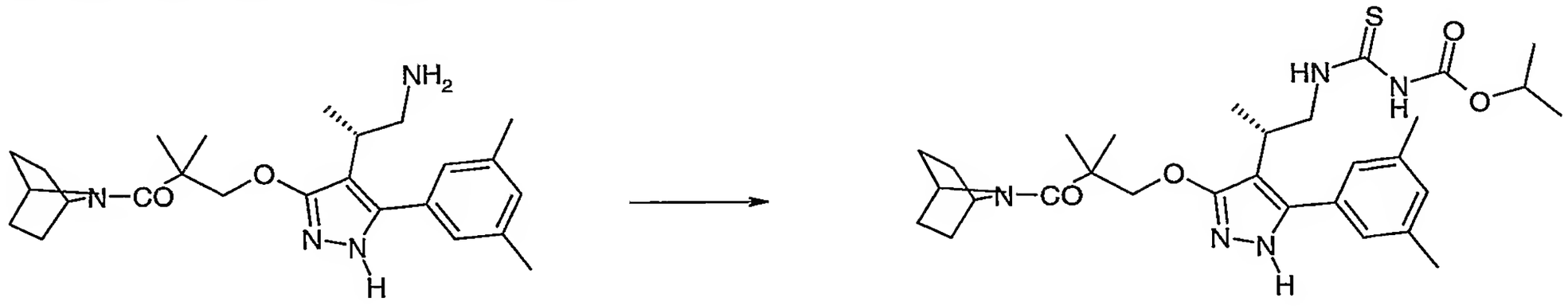
A solution of **CNR** (141 mg ; 0.25 mmol) in CH_2Cl_2 (5 ml) was cooled to 0°C. EDCI (72 mg ; 0.37 mmol) and diisopropylethylamine (65 ul ; 0.37 mmol) were added followed by 4-(3-pyrrolidyl)-pyridine (46 mg ; 0.31 mmol) and the mixture was allowed to warm to room temperature overnight. The mixture was diluted with CH_2Cl_2 and the organic phase was washed with sat. aq. $NaHCO_3$, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 100% EtOAc) to give **Example 5** as a beige solid (128 mg).

Yield : 78%

^{1}H NMR spectrum (DMSO d_6) : 1.05 (m, 6H) ; 1.12 (m, 3H) ; 1.28 (s, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 1.91 (m, 1H) ; 2.2 (m, 1H) ; 2.30 (s, 6H) ; 2.95 (m, 1H) ; 3.2-3.7 (m, 7H) ; 4.17 (s, 2H) ; 4.56 (m, 3H) ; 7.01 (s, 1H) ; 7.04 (s, 1H) ; 7.06 (s, 1H) ; 7.2 (s br, 1H) ; 7.27 (dd, 2H); 8.49 (dd, 2H) ; 11.79 (s, 1H).

MS-ESI : 684 $[M+H]^+$

The starting material **CNR** was prepared as follows:-



Ce (from broad scope) CNR

A solution of **Ce** (150 mg ; 0.35 mmol) in CH_2Cl_2 (5 ml) was cooled to 0°C. A solution of **11** (77 mg ; 0.53 mmol) in CH_2Cl_2 (1 ml) was added and the mixture was allowed to warm to room temperature for 1 h. The mixture was treated with water, diluted with CH_2Cl_2 and the organic phase was washed with brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with EtOAc/CH_2Cl_2 (0-20% EtOAc) to give **CNR** as a gum (141 mg).

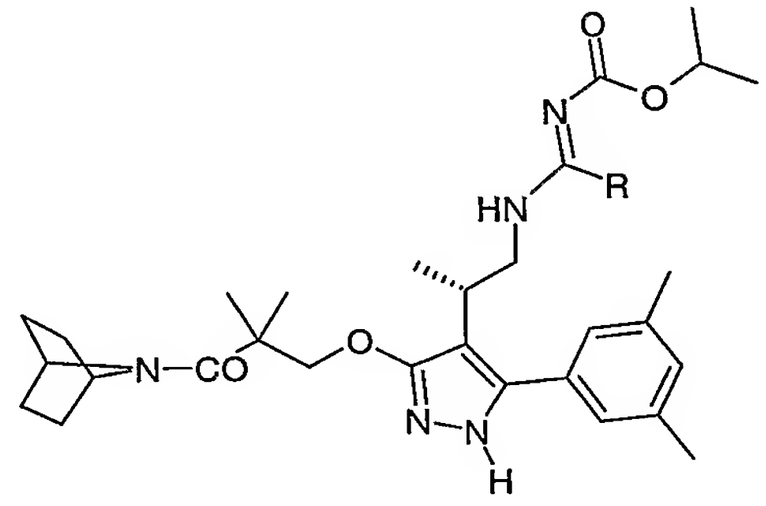
Yield : 70%

^{1}H NMR spectrum (DMSO d_6) : 1.22 (d, 3H) ; 1.8 (m, 6H) ; 1.27 (m, 6H) ;1.41 (m, 4H) ; 1.61 (m, 4H) ; 2.29 (s, 6H) ; 3.06 (q, 1H) ; 3.65 (m, 1H) ; 3.84 (m, 1H) ; 4.19 (m, 2H) ; 4.58 (s, 2H); 4.79 (m, 1H) ; 7.02 (s,1H) ; 7.04 (s, 2H) ; 9.84 (s, 1H) ; 11.8 (s br, 1H).

MS-ESI : 570 $[M+H]^+$

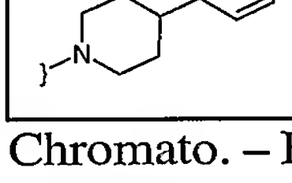
Examples 5.1 – 5.2

The following examples were prepared in a similar manner to Example 5,



the table shows the **R** group relating to the above structure, the reaction conditions and characteristics for each example, corresponding to the description of the preparation of Example 5 given above:-

Example 5.1

R	CNR mg ; mmol	Amine mg ; mmol	EDCI mg ; mmol	DIEA μl ; mmol	Mass mg ; Yield	MS-ESI
	170 ; 0.3	68 ; 0.4	87; 0.45	80 ; 0.45	180 ; 85%	705 $[M+H]^+$

Chromato. – EtOAc/CH_2Cl_2 (0 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 5% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 0.9-1.2 (m, 14H) ; 1.28 (m, 6H) ; 1.43 (m, 4H) ; 1.5 (m, 2H) ; 1.6 (m, 6H) ; 2.31 (s, 6H) ; 2.7 (m, 2H) ; 2.95 (m, 1H) ; 3.2-3.7 (m, 5H) ; 3.75 (m, 2H) ; 3.83 (m, 2H) ; 4.16 (s, 2H) ; 4.57 (m, 3H) ; 7.02 (s, 1H) ; 7.04 (s, 2H) ; 7.46 (s br, 1H) ; 11.80 (s, 1H).

Example 5.2

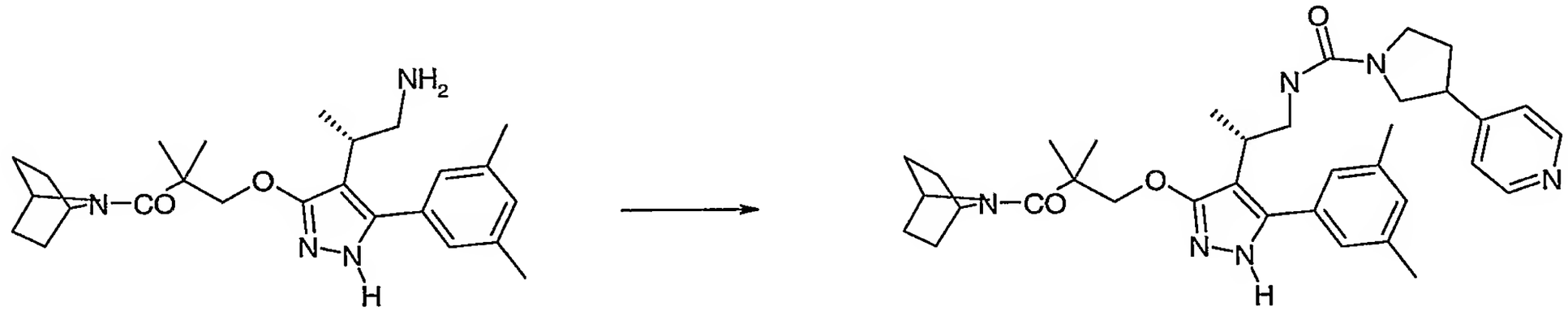
R	CNR mg ; mmol	Amine mg ; mmol	EDCI mg ; mmol	DIEA μl ; mmol	Mass mg ; Yield	MS-ESI
	170 ; 0.3	65 ; 0.4	87; 0.45	80 ; 0.45	172 ; 81%	698 $[M+H]^+$

Chromato. – EtOAc/CH_2Cl_2 (0 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 5% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.07 (m, 6H) ; 1.11 (m, 3H) ; 1.28 (m, 6H) ; 1.42 (m, 4H) ; 1.5 (m, 2H) ; 1.62 (m, 4H) ; 1.72 (m, 2H) ; 2.30 (s, 6H) ; 2.7 (m, 1H) ; 2.9 (m, 2H) ; 2.95 (m, 1H) ; 3.2-3.4 (m, 2H) ; 3.85 (m, 2H) ; 4.17 (m, 2H) ; 4.57 (m, 3H) ; 7.01 (s, 1H) ; 7.06 (s, 2H); 7.18 (d, 2H) ; 7.5 (s br, 1H) ; 8.45 (d, 2H) ; 11.81 (s, 1H).

Example 6

3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.1]heptan-7-yl)propoxy]-4-[1S-methyl-2-(3-pyridin-4-ylpyrrolidin-1-carboxamido)ethyl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole



Ce (from broad scope) Example 6

A solution of **Ce** (170 mg ; 0.4 mmol) in CH_2Cl_2 (5 ml) was cooled to 0°C and DIEA (140 µl ; 0.8 mmol) was added. A solution of 4-nitrophenyl chloroformate (85 mg ; 0.42 mmol) in CH_2Cl_2 (1 ml) was added and the mixture was allowed to stir for 30 min. 4-(3-Pyrrolidyl)-pyridine (71 mg ; 0.48 mmol) was added and the mixture allowed to warm to room temperature for 1 h. The mixture was directly purified by flash chromatography eluting with MeOH/CH_2Cl_2 (0-10% MeOH) to give **Example 6** as a pale yellow powder (212 mg).

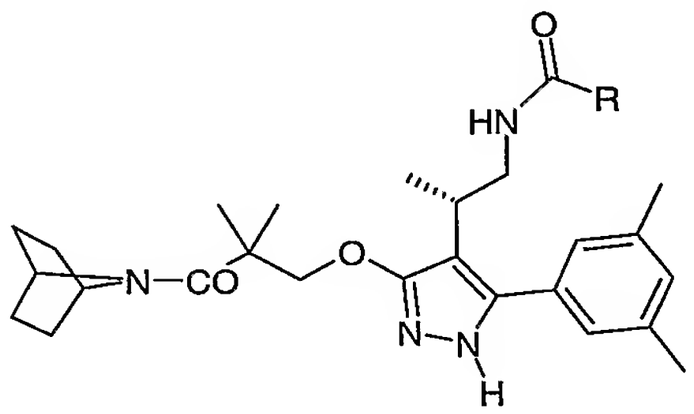
Yield : 88%

^{1}H NMR spectrum (DMSO d_6) : 1.11 (m, 3H) ; 1.28 (m, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 1.95 (m, 1H) ; 2.22 (m, 1H) ; 2.29 (s, 6H) ; 2.93 (m, 1H) ; 3.2-3.7 (m, 6H) ; 3.67 (m, 1H) ; 4.17 (s, 2H) ; 4.58 (s, 2H) ; 6.21 (m, 1H) ; 7.00 (s, 1H) ; 7.14 (s, 2H) ; 7.26 (m, 2H) ; 8.47 (m, 2H) ; 11.79 (s, 1H).

MS-ESI : 599 $[M+H]^+$

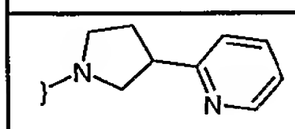
Examples 6.1 – 6.

The following examples were prepared in a similar manner to Example 6,



the table shows the **R** group relating to the above structure, the reaction conditions and characteristics for each example, corresponding to the description of the preparation of Example 6 given above:-

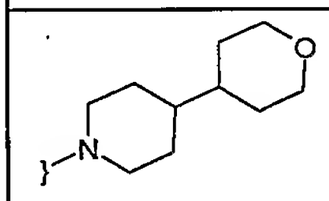
Example 6.1

R	Ce mg ; mmol	DIEA μl ; mmol	4-NPC mg ; mmol	Amine mg ; mmol	Mass mg ; Yield	MS-ESI
	170 ; 0.4	140 ; 0.8	90 ; 0.42	71 ; 0.48	226 ; 94%	599 $[M+H]^+$

Chromato. –MeOH/ EtOAc (0 to 5% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.11 (m, 3H) ; 1.28 (m, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 1.99 (m, 1H) ; 2.20 (m, 1H) ; 2.29 (s, 6H) ; 2.93 (m, 1H) ; 3.2-3.5 (m, 6H) ; 3.68 (m, 1H) ; 4.17 (s, 2H) ; 4.58 (s, 2H) ; 6.15 (m, 1H) ; 7.00 (s, 1H) ; 7.14 (m, 2H) ; 7.24 (m, 1H) ; 7.29 (m, 1H) ; 7.72 (m, 1H) ; 8.49 (m, 1H) ; 11.74 (s, 1H).

Example 6.2

R	Ce mg ; mmol	DIEA μl ; mmol	4-NPC mg ; mmol	Amine mg ; mmol	Mass mg ; Yield	MS-ESI
	110 ; 0.26	90 ; 0.52	55; 0.27	52 ; 0.28	131 ; 81%	620 $[M+H]^+$

Chromato. – EtOAc/CH_2Cl_2 (0 to 100% EtOAc)

^{1}H NMR spectrum (DMSO d_6) : 0.9 (m, 2H) ; 1.07 (m, 3H) ; 1.14 (m, 4H) ; 1.28 (m, 6H) ; 1.4-1.7 (m, 12H) ; 2.30 (s, 6H) ; 2.9 (m, 1H) ; 3.2-3.4 (m, 6H) ; 3.82 (m, 2H) ; 3.96 (m, 2H) ; 4.17 (m, 2H) ; 4.58 (m, 2H) ; 6.45 (m, 1H) ; 6.99 (s, 1H) ; 7.14 (s, 2H) ; 11.81 (s, 1H).

THERAPEUTIC USES

Compounds of Formula (I) are provided as medicaments for antagonising gonadotropin releasing hormone (GnRH) activity in a patient, eg, in men and/or women. To this end, a compound of Formula (I) can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier (eg, water). The formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg, lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of 0.1mgkg^{-1} to 30mgkg^{-1} (preferably, 5mgkg^{-1} to 20mgkg^{-1}) of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

Buffers, pharmaceutically acceptable co-solvents (eg, polyethylene glycol, propylene glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

One aspect of the invention relates to the use of compounds according to the invention for reducing the secretion of LH and/or FSH by the pituitary gland of a patient. In this respect, the reduction may be by way of a reduction in biosynthesis of the LH and FSH and/or a reduction in the release of LH and FSH by the pituitary gland. Thus, compounds according to the invention can be used for therapeutically treating and/or preventing a sex hormone related condition in the patient. By "preventing" we mean reducing the patient's risk of contracting the condition. By "treating" we mean eradicating the condition or reducing its severity in the patient. Examples of sex hormone related conditions are: a sex hormone dependent cancer, benign prostatic hypertrophy, myoma of the uterus, endometriosis, polycystic ovarian disease, uterine fibroids, prostatauxe, myoma uteri, hirsutism and precocious puberty. Examples of sex hormone dependent cancers are: prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The compounds of the invention may be used in combination with other drugs and therapies used to treat / prevent sex-hormone related conditions.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

In the field of medical oncology examples of such combinations include combinations with the following categories of therapeutic agent:

i) anti-angiogenic agents (for example linomide, inhibitors of integrin αvβ3 function, angiostatin, endostatin, razoxin, thalidomide) and including vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (RTKIs) (for example those described in international patent applications publication nos. WO-97/22596, WO-97/30035, WO-97/32856 and WO-98/13354, the entire disclosure of which documents is incorporated herein by reference);

ii) cytostatic agents such as anti-oestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), anti-progestogens, anti-androgens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example epidermal growth factor (EGF), platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);

iii) biological response modifiers (for example interferon);

iv) antibodies (for example edrecolomab); and

v) anti-proliferative/anti-neoplastic drugs and combinations thereof, as used in medical oncology, such as anti-metabolites (for example anti-folates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); anti-tumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); anti-mitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, irinotecan).

The compounds of the invention may also be used in combination with surgery or

radiotherapy.

ASSAYS

The ability of compounds according to the invention to act as antagonists of GnRH can be determined using the following in vitro assays.

Binding Assay Using Rat pituitary GnRH Receptor

The assay is performed as follows:-

1. Incubate crude plasma membranes prepared from rat pituitary tissues in a Tris.HCl buffer (pH. 7.5, 50 mM) containing bovine serum albumin (0.1%), [I-125]D-t-Bu-Ser6-Pro9-ethyl amide-GnRH, and the test compound. Incubation is at 4°C for 90 minutes to 2 hours.
2. Rapidly filter and repeatedly wash through a glass fibre filter.
3. Determine the radioactivity of membrane bound radio-ligands using a gamma counter.

From this data, the IC_{50} of the test compound can be determined as the concentration of the compound required to inhibit radio-ligand binding to GnRH receptors by 50%. Compounds according to the present invention have activity at a concentration from 1nM to 5 μM.

Binding Assay Using Human GnRH Receptor

Crude membranes prepared from CHO cells expressing human GnRH receptors are sources for the GnRH receptor. The binding activity of compounds according to the invention can be determined as an IC_{50} which is the compound concentration required to inhibit the specific binding of [^{125}I]buserelin to GnRH receptors by 50%. [^{125}I]Buserelin (a peptide GnRH analogue) is used here as a radiolabelled ligand of the receptor.

Assay to Determine Inhibition of LH release

The LH release assay can be used to demonstrate antagonist activity of compounds, as demonstrated by a reduction in GnRH-induced LH release.

Preparation of Pituitary Glands

Pituitary glands obtained from rats are prepared as follows. Suitable rats are Wistar male rats (150-200g) which have been maintained at a constant temperature (eg, 25°C) on a

12 hour light/12 hour dark cycle. The rats are sacrificed by decapitation before the pituitary glands are aseptically removed to tube containing Hank's Balanced Salt Solution (HBSS). The glands are further processed by:-

1. Centrifugation at 250 x g for 5 minutes;
2. Aspiration of the HBSS solution;
3. Transfer of the glands to a petri dish before mincing with a scalpel;
4. Transfer of the minced tissue to a centrifuge tube by suspending the tissue three successive times in 10 ml aliquots of HBSS containing 0.2% collagenase and 0.2% hyaluronidase;
5. Cell dispersion by gentle stirring of the tissue suspension while the tube is kept in a water bath at 37°C;
6. Aspiration 20 to 30 times using a pipette, undigested pituitary fragments being allowed to settle for 3 to 5 minutes;
7. Aspiration of the suspended cells followed by centrifugation at 1200 x g for 5 minutes;
8. Re-suspension of the cells in culture medium of DMEM containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids, 1% glutamine and 0.1% gentamycin;
9. Treatment of the undigested pituitary fragments 3 times with 30 ml aliquots of the collagenase and hyaluronidase;
10. Pooling of the cell suspensions and dilution to a concentration of 3×10^5 cells/ml;
11. Placing of 1.0ml of this suspension in each of a 24 well tray, with the cells being maintained in a humidified 5% CO_2/95% air atmosphere at 37°C for 3 to 4 days

Testing of Compounds

The test compound is dissolved in DMSO to a final concentration of 0.5% in the incubation medium.

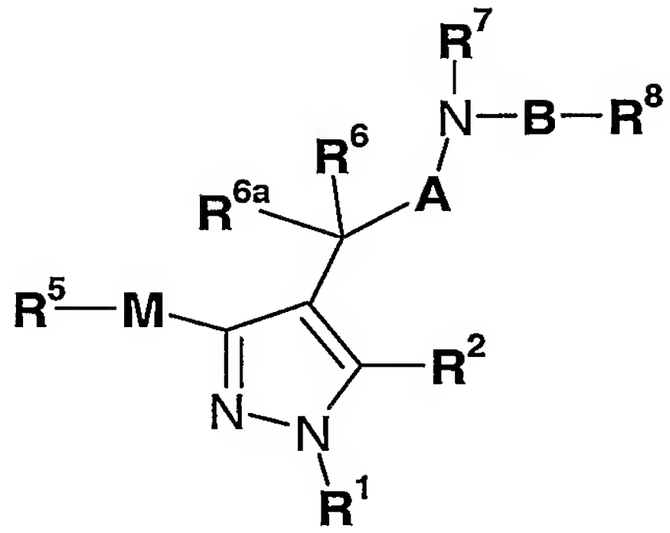
1.5 hours prior to the assay, the cells are washed three times with DMEM containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids (100X), 1% glutamine (100X), 1% penicillin/streptomycin (10,000 units of each per ml) and 25 mM HEPES at pH 7.4. Immediately prior to the assay, the cells are again washed twice in this medium .

Following this, 1ml of fresh medium containing the test compound and 2nM GnRH is added to two wells. For other test compounds (where it is desired to test more than one compound), these are added to other respective duplicate wells. Incubation is then carried out at 37°C for three hours.

Following incubation, each well is analysed by removing the medium from the well and centrifuging the medium at 2000 x g for 15 minutes to remove any cellular material. The supernatant is removed and assayed for LH content using a double antibody radio-immuno assay. Comparison with a suitable control (no test compound) is used to determine whether the test compound reduces LH release. Compounds according to the present invention have activity at a concentration from 1nM to 5 μM.

CLAIMS:

1. A compound of Formula (I),

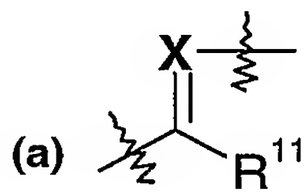


Formula (I)

wherein

A represents a direct bond or optionally substituted C_{1-5}alkylene;

B is a group of Formula (II):



Formula (II);

wherein at position (a) Formula (II) is attached to the nitrogen atom and the group **X** is attached to $\mathbf{R^8}$;

M is $-(CH_2)_{0-2}$-O-;

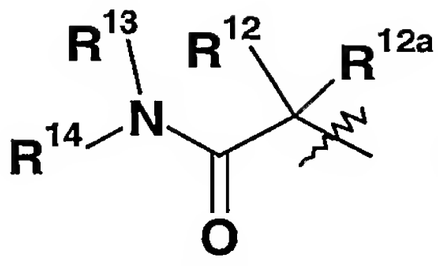
$\mathbf{R^1}$ represents hydrogen; optionally substituted C_{1-8}alkyl; or $(CH_2)_{\mathbf{b}}$-$\mathbf{R^a}$, wherein

$\mathbf{R^a}$ represents C_{3-8}cycloalkyl and **b** is zero or an integer from 1 to 6;

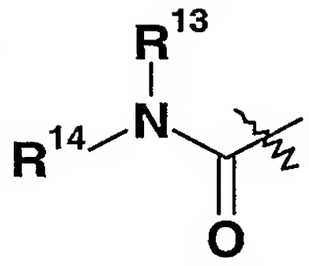
$\mathbf{R^2}$ represents an optionally substituted mono- or bi-cyclic aromatic ring structure wherein the optional substituents are selected from cyano, N$\mathbf{R^3R^{3a}}$, optionally substituted C_{1-8}alkyl, optionally substituted C_{1-8}alkoxy or halo;

$\mathbf{R^3}$ and $\mathbf{R^{3a}}$ are independently selected from hydrogen; optionally substituted C_{1-8}alkyl and optionally substituted aryl;

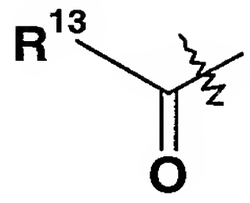
$\mathbf{R^5}$ is selected from an optionally substituted 3 to 8 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S; or a group of formula **III-a**; **III-b**; **III-c**; **III-d**; **III-e; III-f, III-g , III-h**, **III-i** or: **III-j**;



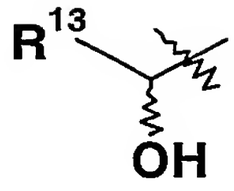
III-a



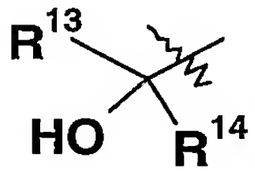
III-b



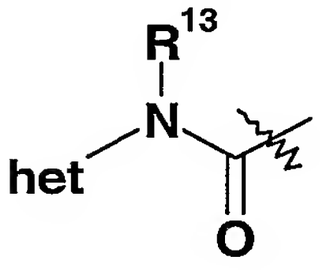
III-c



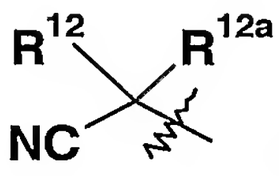
III-d



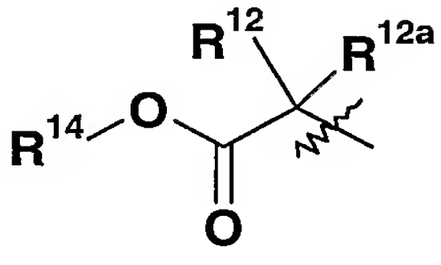
III-e



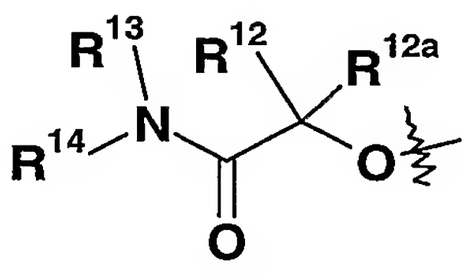
III-f



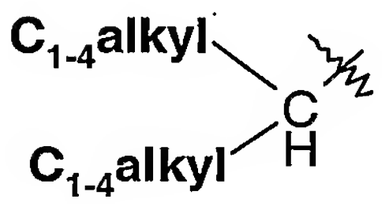
III-g



III-h



III-i



III-j

wherein **het** represents an optionally substituted 3 to 8 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

$\mathbf{R^6}$ and $\mathbf{R^{6a}}$, are independently selected from hydrogen and optionally substituted C_{1-8}alkyl; or $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ together represent carbonyl;

$\mathbf{R^7}$ represents hydrogen or optionally substituted C_{1-8}alkyl;

or  together from an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 3 further heteroatoms independently selected from O, N and S, and $\mathbf{R^{6a}}$ represents hydrogen and optionally substituted C_{1-8}alkyl;

X and $\mathbf{R^8}$ are selected from:

(i) **X** represents N and $\mathbf{R^8}$ is selected from:

cyano, hydrogen, hydroxy, -O-$\mathbf{R^b}$, –N$\mathbf{R^b R^c}$ –C(O)O-$\mathbf{R^b}$, –CON$\mathbf{R^b R^c}$ or NH-C(O)-$\mathbf{R^b}$, where $\mathbf{R^b}$ and $\mathbf{R^c}$ are independently selected from hydrogen and C_{1-4}alkyl optionally substituted with hydroxy, amino, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, HO-C_{2-4}alkyl-NH- or HO-C_{2-4}alkyl-N(C_{1-4}alkyl)-;

(ii) **X** represents CH and $\mathbf{R^8}$ represents NO_2; and

(iii) **X**- $\mathbf{R^8}$ represents –O-;

$\mathbf{R^{11}}$ is a group of the formula: N($\mathbf{R^9 R^{10}}$) wherein $\mathbf{R^9}$ represents hydrogen, aryl, an optionally substituted 3- to 10 membered heterocyclic ring or optionally-substituted

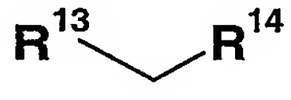
C_{1-8}alkyl and $\mathbf{R^{10}}$ represents hydrogen or optionally substituted C_{1-8}alkyl; or the structure N($\mathbf{R^9R^{10}}$) represents an optionally-substituted 3- to 10 membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;

$\mathbf{R^{12}}$ and $\mathbf{R^{12a}}$ are independently selected from hydrogen or optionally substituted C_{1-8}alkyl; or $\mathbf{R^{12}}$ and $\mathbf{R^{12a}}$ together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring;

$\mathbf{R^{13}}$ and $\mathbf{R^{14}}$ are selected from:

(i) $\mathbf{R^{13}}$ is selected from hydrogen; optionally substituted C_{1-8}alkyl; optionally substituted aryl; -$\mathbf{R^d}$-Ar, where $\mathbf{R^d}$ represents C_{1-8}alkylene and Ar represents optionally substituted aryl; and optionally substituted 3 to 8 membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and $\mathbf{R^{14}}$ is selected from hydrogen; optionally substituted C_{1-8}alkyl and optionally substituted aryl;

(ii) where $\mathbf{R^5}$ represents a group of formula **III-a , III-b** or **III-i**, then the group N$\mathbf{R^{13}}$(-$\mathbf{R^{14}}$) represents an optionally substituted 3 to 8 membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

(iii) where $\mathbf{R^5}$ represents structure **III-e**, then the group  represents an optionally substituted 3 to 8 membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

or a salt, pro-drug or solvate thereof.

2. A compound according to Claim 1 wherein $\mathbf{R^9}$ represents hydrogen, optionally substituted aryl, an optionally substituted 3- to 10 membered heterocyclic ring or optionally-substituted C_{1-8}alkyl and

$\mathbf{R^{10}}$ represents hydrogen or optionally substituted C_{1-8}alkyl

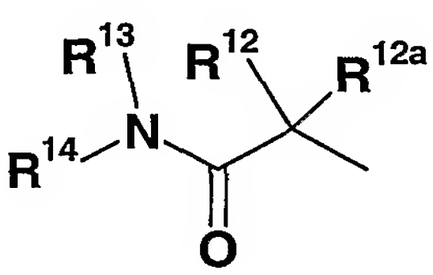
wherein the optional substituents on aryl, the heterocyclic ring and C_{1-8}alkyl are selected from: hydroxy, amino, nitro, cyano, optionally-substituted aryl, optionally substituted 3 to 8 membered heterocyclyl containing from 1 to 4 heteroatoms independently selected from O, N and S, -O-$\mathbf{R^b}$, C(O)N$\mathbf{R^bR^c}$, -N$\mathbf{R^bR^c}$, -N$\mathbf{R^c}$C(O)-$\mathbf{R^b}$, -C(O)N$\mathbf{R^bR^c}$, -N$\mathbf{R^c}$S(O_{0-2})$\mathbf{R^b}$, -S(O_{0-2})$\mathbf{R^b}$, wherein $\mathbf{R^b}$ and $\mathbf{R^c}$ are as defined in Claim 1.

3. A compound according to Claim 2 wherein $\mathbf{R^9}$ is a C_{1-6}alkyl group substituted by pyridyl, thienyl, piperidinyl, imidazolyl, triazolyl, thiazolyl, pyrrolidinyl, piperazinyl, morpholinyl, imidazolinyl, benztriazolyl, benzimidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl, furanyl, pyrrolyl, 1,3-dioxolanyl or 2-azetinyl, each of which is optionally substituted.

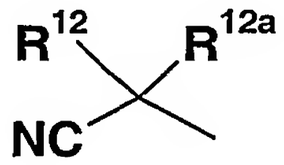
4. A compound according to Claim 1 wherein the structure N($\mathbf{R^9R^{10}}$) represents an optionally-substituted 3- to 10 membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S.

5. A compound according to Claim 4 wherein the 3- to 10 membered heterocyclic ring is optionally substituted by one of more groups selected from $\mathbf{R^{15}}$ wherein $\mathbf{R^{15}}$ is selected from optionally substituted aryl, an optionally substituted 3 to 10 membered heterocyclic ring or optionally substituted C_{1-4}alkyl
wherein the optional substituents on aryl, a heterocyclic ring or C_{1-4}alkyl are selected from: hydroxy, amino, nitro, cyano, optionally-substituted aryl, optionally substituted 3 to 8 membered heterocyclyl containing from 1 to 4 heteroatoms independently selected from O, N and S, -O-$\mathbf{R^b}$, C(O)N$\mathbf{R^bR^c}$, -N$\mathbf{R^bR^c}$, -N$\mathbf{R^c}$C(O)-$\mathbf{R^b}$, -C(O)N$\mathbf{R^bR^c}$, -N$\mathbf{R^c}$S(O_{0-2})$\mathbf{R^b}$, -S(O_{0-2})$\mathbf{R^b}$, wherein $\mathbf{R^b}$ and $\mathbf{R^c}$ are as defined in Claim 1.

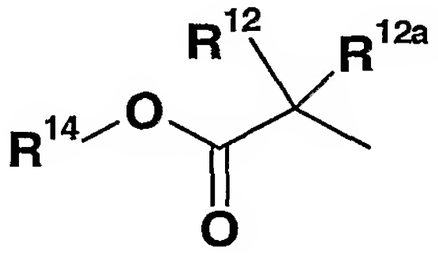
6. A compound according to any one of the preceding claims wherein $\mathbf{R^5}$ is selected from a group of formula **III-a** , **III-g**, **III-h**, **III-i** or **III-j**:



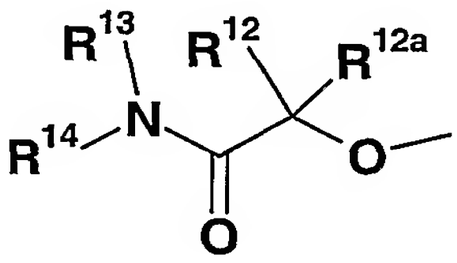
III-a



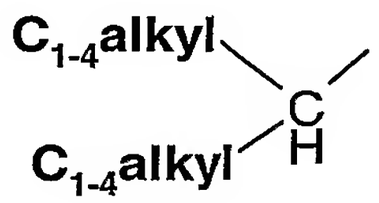
III-g



III-h



III-i



III-j

7. A compound according to any one of the preceding claims wherein **X** and $\mathbf{R^8}$ are selected from

(a) **X** represents N and $\mathbf{R^8}$ represents cyano or –C(O)O-$\mathbf{R^b}$; or

(b) **X** represents N and $\mathbf{R^8}$ represents hydrogen.

8. A compound according to any one of the preceding claims wherein $\mathbf{R^2}$ is selected from an optionally substituted monocyclic aromatic ring structure wherein the optional substituents are selected from cyano, N$\mathbf{R^e R^f}$, optionally substituted $C_{1\text{-}8}$alkyl, optionally substituted $C_{1\text{-}8}$alkoxy or halo wherein $\mathbf{R^e}$ and $\mathbf{R^f}$ are independently selected from hydrogen, $C_{1\text{-}6}$alkyl or aryl.

9. A compound according to any one of the preceding claims wherein $\mathbf{R^1}$ is hydrogen.

10. The compound:

3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.1]heptan-7-yl)propyl]-4-[1S-methyl-2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-yl carboximidamido) ethyl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole;

or a salt, pro-drug or solvate thereof.

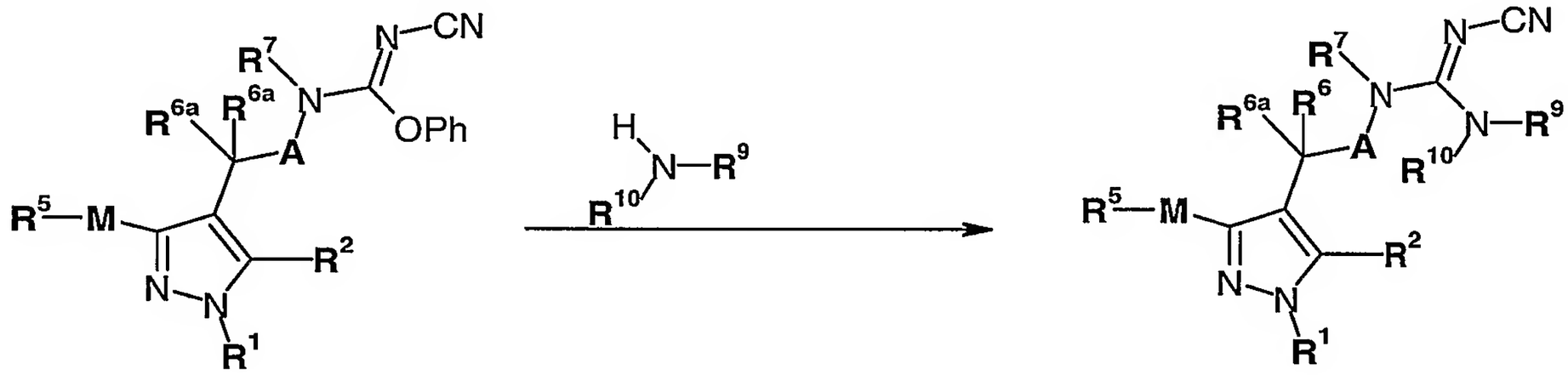
11. A compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10 for use as a medicament.

12. A pharmaceutical formulation comprising a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10 and a pharmaceutically acceptable diluent or carrier.

13. Use of a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10, in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.

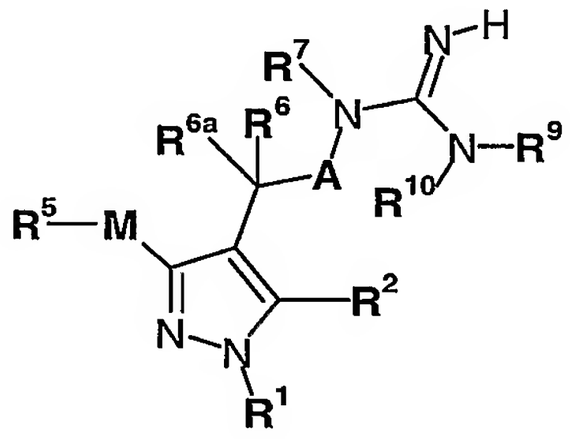
14. A process of producing a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10, wherein the process comprises a reaction step selected from any one of steps (a) to (f):-

(a) for compounds wherein **X** is N and $\mathbf{R^8}$ is CN, reaction of a compound of formula **XXXII** as follows



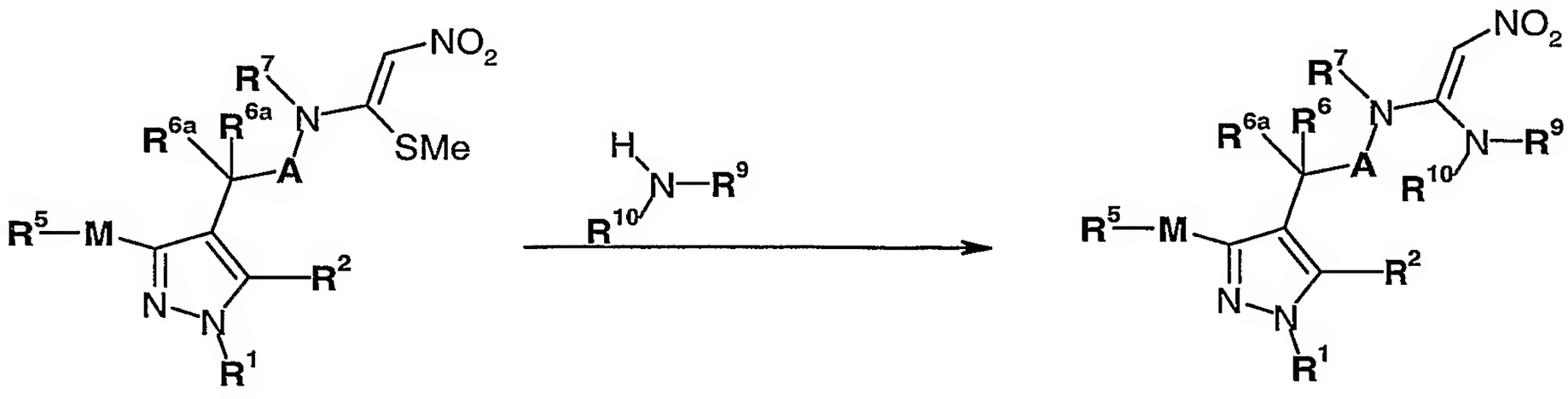
XXXII **XXXIII**

(b) for compounds wherein **X** is N and $\mathbf{R^8}$ is hydrogen, cleavage of the cyano group of compound of formula **XXXIII** in the presence of acid to produce compound of formula **XXXIV**



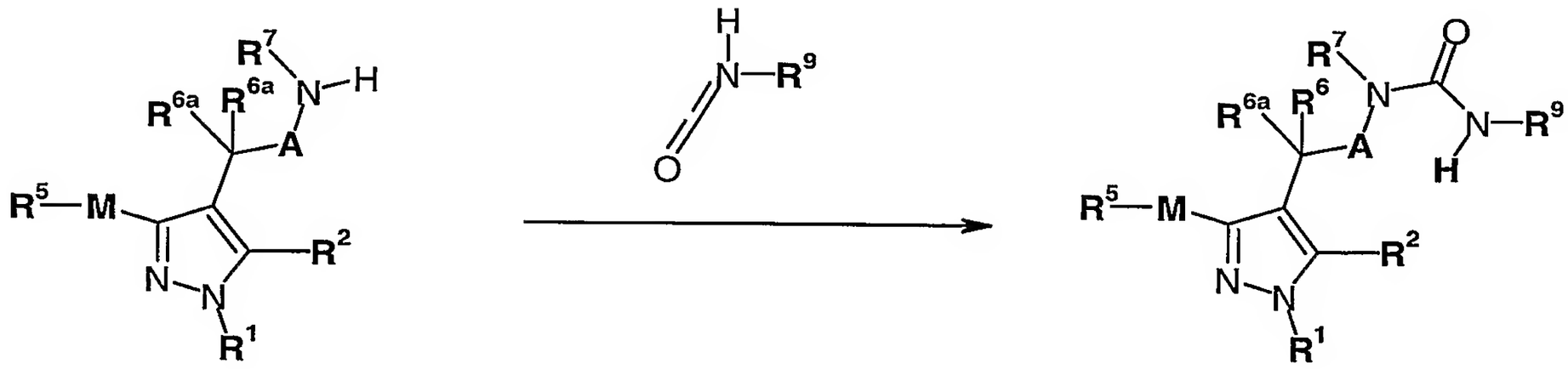
XXXIV

(c) for compounds wherein **X** is CH and $\mathbf{R^8}$ is NO_2, reaction of compound of formula **XXXV** as follows



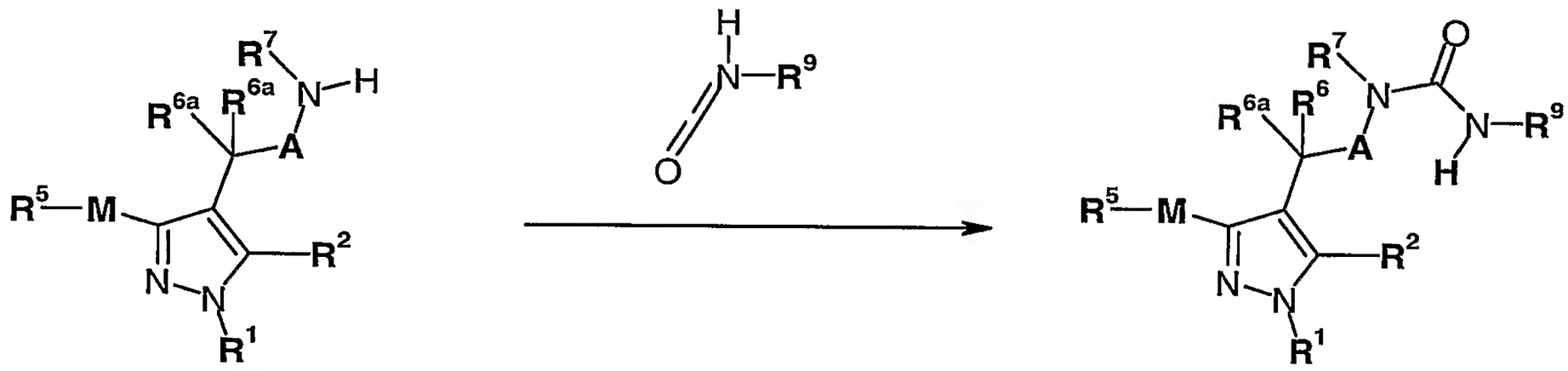
XXXV **XXXVI**

(d) for compounds where **X-R^8** is O, reaction of compound of formula **XXXVII** as follows



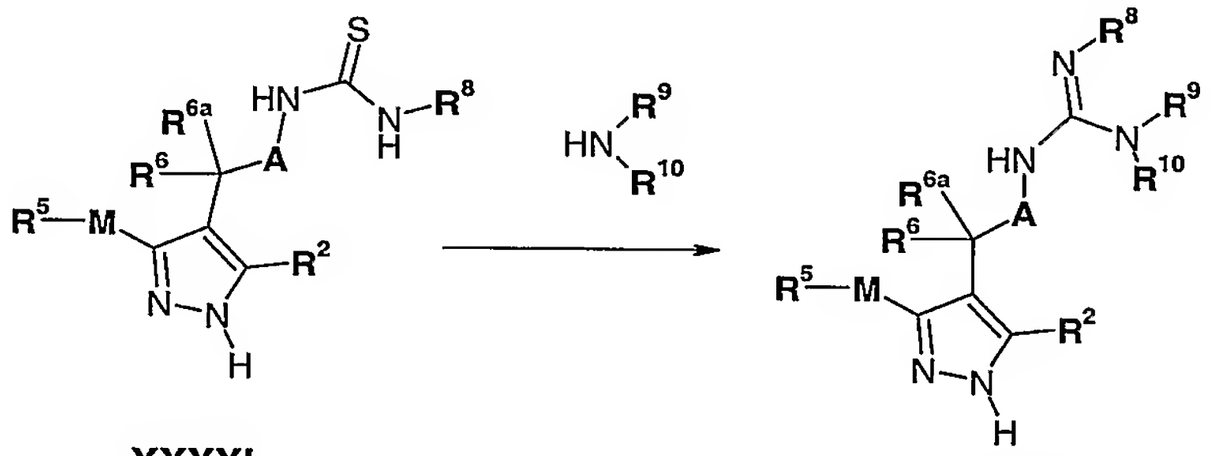
XXXIX **XXXX**

(e) for compounds where **X-R^8** is O, reaction of compound of formula **XXXIX** as follows



XXXIX **XXXX**

(f) to form a compound wherein **X** is nitrogen reaction of a compound of formula XXXXI as follows



XXXXI **XXXXII**

and thereafter if necessary:

i) converting a compound of the Formula (I) into another compound of the Formula (I);

ii) removing any protecting groups;

iii) forming a salt, pro-drug or solvate.

INTERNATIONAL SEARCH REPORT

Internati application No
PCT/GB 03/03623

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 C07D487/08 A61K31/4155

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 04013 A (PONPIPOM MITREE M ;WYVRATT MATTHEW J (US); CHU LIN (US); GOULET MA) 27 January 2000 (2000-01-27) page 2, line 20 - line 24 example 3.1 claim 1 ---	1,13
A	WO 97 44339 A (GOULET MARK ;JIANG JINLONG (US); ALLEN ERIC E (US); DEVITA ROBERT) 27 November 1997 (1997-11-27) page 3, line 20 - line 24 example 1D claim 1 ----	1,13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2003	27/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fanni, S

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatic pplication No
PCT/GB 03/03623

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